MD Anderson IND Sponsor Cover Sheet	
Protocol ID	2017-0337
Protocol Title	An Open-label Phase IB/II Multi-arm Study of OX40 agonist monoclonal antibody (mAb), anti-PDL1 mAb, smoothened inhibitor, anti-CD33 mAb, Bcl-2 inhibitor, and azacitidine as single-agents and/or combinations for the Treatment of Patients with Acute Myeloid Leukemia (AML)
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Protocol PI	Naval Daver, M.D.
Department	Leukemia
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An Open-label Phase IB/II Multi-arm Study of OX40 agonist monoclonal antibody (mAb), anti-PDL1 mAb, smoothened inhibitor, anti-CD33 mAb, Bcl-2 inhibitor, and azacitidine as single-agents and/or combinations for the Treatment of Patients with Acute Myeloid Leukemia (AML)

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Sponsor: University of Texas, MD Anderson Cancer Center

IND number: 136570

University of Texas

MD Anderson Cancer Center

Leukemia Department, Unit 428

1.0 OBJECTIVES

1.1 Primary Objectives

1. To evaluate the safety of multiple combination regimens of IO-agents [PF04518600 (Ox40 agonist mAb), avelumab (PD-L1 antagonist mAb)], hypomethylator therapy (azacitidine), anti CD33 mAb (gemtuzumab ozogamycin, GO), Bcl-2 inhibitor (venetoclax) and smoothened pathway inhibitor (glasdegib) in patients with relapsed/refractory (RR) AML.

2. To evaluate the composite complete response (CRc) defined as CR + complete response with incomplete recovery of platelets (CRp) + complete response with incomplete recovery of counts (CRi) within 3 months of therapy initiation in patients with RR AML of:
Arm A. PF-04518600 alone,
Arm B. Azacitidine + venetoclax + GO
Arm C. Azacitidine + avelumab +GO
Arm D. Azacitidine + venetoclax + avelumab
Arm E. Azacitidine + avelumab + PF-04518600,
Arm F. GO + glasdegib

1.2 Secondary Objectives:

-To assess the morphologic leukemia free survival (MLFS), partial response (PR), hematologic improvement (HI) rate of patients with RR AML treated on arms A – F
-To assess relapse-free survival (RFS), time to next therapy (TNT), 4-week and 8-week mortality, and overall survival (OS) of patients with RR AML treated on arms A – F.
-To assess minimal residual disease (MRD) by multiparametric flow-cytometry at response (+/- 1 month) and assess correlation of MRD to OS in arms A – F.

1.3 Exploratory Objectives:

1. To study immunological and molecular features at baseline and at predefined time-points on-therapy with each combination in the peripheral blood and bone marrow to include: (a) quantification of immune ligand expression by the AML/MDS blasts and AML/MDS stromal components (MDSCs, monocytes and MSCs) including galectin 9, 4-1BBL, ICOSL, PD-L1, PD-L2, OX-40L, CD137L, others and (b) determination of the quantitative expression of positive and negative co-stimulatory molecules including 4-1BB, CTLA-4, ICOS, PD-1, OX40, LAG-3, TIM-3, HLA-DR, Ki67, others on T-lymphocyte subsets and (c) identification of the immunophenotype of tumor-infiltrating T-lymphocytes (TILs) pre- and post-therapy including CD8+, CD4+ effector, CD4+ regulatory TILs and central memory, effector memory, and naïve T-cell subsets among the CD4 and CD8 populations. These analysis will be done using multiparametric flow-cytometry (MFC) or multi-stain immunohistochemistry (IHC)

2. To develop a micro-array based gene expression profile (GEP) predictor of response to the immune combinations using either baseline RNA sequencing and/or nanostring.

3. To perform a validated NGS-based analysis for the detection of somatic mutations in the coding sequences of 28 genes commonly mutated in AML at baseline and on treatment to identify baseline predictors and clonal evolution on treatment and/or whole exome sequencing (WES) in selected cases.

4. To identify clonal T-cells by performing T-cell repertoire analysis at baseline and longitudinally on therapy on the peripheral blood and/o bone marrow samples.

5. To assess levels of cytokines at baseline and longitudinally on therapy in peripheral blood and/or bone marrow.

2.0 BACKGROUND

2.1 RELAPSED/REFRACTORY AML

Therapy for AML has improved only modestly over the last four decades. Traditional induction chemotherapy produces cure rates of 30% in adults with AML[1-3]. Patients with relapsed AML have an overall survival of 1 to 4 months with standard salvage therapy [4,5]. We have previously reported a dismal median OS (3.8 months) for patients with AML who are refractory to high-dose cytarabine (HiDAC)-containing induction therapy (defined as ≥ 1gm/m^2 cytarabine per dose). Salvage therapy in such patient populations yielded a response rate of 18% and median OS of 4.5 months. The preliminary data from investigators in our group[6] and from others [7,8] suggest that immune therapies may be a crucial third modality in combination with cytotoxic and/or targeted molecular therapy to produce deeper and/or more durable responses in AML and myelodysplastic syndrome (MDS).

2.2 IMMUNOTHERAPY IN LEUKEMIA

Although the role of antibodies that target PD-1 and other checkpoint pathways has been established in solid tumor malignancies and FDA approved for melanoma and non-small cell lung cancer, there remains a very limited experience in incorporating immune checkpoint modulating agents in the therapy of leukemias. This is surprising for many reasons. First, leukemias are the quintessential immune responsive tumor type, as proven by the success of allogeneic stem cell transplantation (allo-SCT). Second, having an immune cell lineage, leukemias often express immune checkpoint molecules that are absent in solid tumor cells thereby offering direct targets for immune checkpoint inhibition. Third, a number of studies have demonstrated encouraging results with immune checkpoint inhibition in other hematologic malignancies including: Hodgkin's lymphoma, follicular lymphoma, diffuse large B-cell lymphoma, and multiple myeloma[9,10]

2.2.1 Role of PD-1/PD-L1 interactions in AML

A major anti-tumor inhibitory mechanism is up-regulation of programmed death-ligand 1 (PD-L1) on tumor or stromal cells or tumor infiltrating lymphocytes (TILs), which binds to programmed death-1 (PD-1) on activated CD8+ T cells [11-14]. The PD-1/PD-L1 pathway has been shown to play a major role in immune evasion and cytotoxic T-cell exhaustion in hematologic malignancies including AML and MDS and may be associated with AML progression [7,8,15,16]. Activation of PD-1 results in in immune evasion and exhaustion of tumor-infiltrating CD8+ cytotoxic T-lymphocytes (CTLs) in human and murine AML [7]. Zhang et al. noted that elevated PD-1/PD-L1 expression significantly blunted the anti-leukemic effects of CD8$^+$ CTLs in murine AML models [7]. Anti-PD1 and/or anti-PD-L1 antibodies augmented anti-tumor CD8$^+$ CTL responses by preventing CD8$^+$ exhaustion, resulting in decreased AML burden in the blood and other organs, and increased survival in mice. Zhou et al have demonstrated that AML progression in a murine model

is associated with elevated PD-1 expression on CTLs and increased T-regulatory cells at the tumor site[8]. Both these mechanism decrease CTL activity at the tumor site. Elevated PD- 1 expression independently dampens the anti-leukemic effect of CTLs. T-regulatory cells (Tregs) further suppress CTL activity and this suppression depends on PD-1 expression by Tregs and PD-L1 expression by antigen-presenting cells. Anti-PD-L1 monoclonal antibody treatment increased the proliferation and function of CTLs at tumor sites by reducing the interaction between PD1 and PDL1 resulting in decreased Treg-mediated suppression of CTLs. The enhanced CTL activity resulted in reduced AML tumor burden, and resulted in long-term murine survivors.

Our group analyzed 124 patients with MDS/AML and noted that patients with lower PD-L1 expression had a non-significant trend toward better OS (31.5 versus 16.2 months, *P*=0.24) [6]. Patients with a greater degree of up regulation of these checkpoint molecules had a higher propensity for resistance to epigenetic therapy. Bone marrow samples from healthy donors were used as control for these studies. Chen et al found increased expression of PD-L1 at AML progression, which was an independent negative prognostic factor for French-American-British type M5 AML[17] . Another confirmation of the negative impact of PD-L1 overexpression in patients with AML was obtained by interrogating the NEJM TCGA data by cBioportal. Patients with AML with increased PD-L1 mRNA had an inferior OS. Thirdly, in leukemia, PD-1 and CTLA4 have been shown to play a role in leukemia, and graft versus host disease (GvHD), and their overexpression was clearly associated with a more aggressive leukemia[16]

The role of other checkpoint pathways including OX40 in AML/MDS has not been published in functional studies. However, we have developed expression data for these checkpoint pathways in 75 AML patients in collaboration with the immunotherapy-platform at MDACC (Pam Sharma, Jim Allison).

2.2.2 PD1, PD-L1, OX40, 4-1BB and other immune checkpoint receptor expression in AML (Data from Department of Leukemia and Immunotherapy Platform, MDACC)

To define the immune landscape of AML we performed 17-color multi-parametric flow-cytometry (MFC) on BM aspirates from 36 patients with untreated AML and 39 patients with relapsed AML to assess the expression of costimulatory ligands (4-1BBL, B7-1, B7-2, ICOSL, PD-L1, PD-L2, OX40L) on leukemic blasts and the costim receptors (4-1BB, CTLA-4, ICOS, PD-1, OX40, GITR, LAG-3, TIM-3) on T cell subsets: CD4 T effector cells [Teff]: $CD3^+CD4^+CD127^{lo/+}Foxp3^-$, CD4 T regulatory cells [Treg]: $CD3^+CD4^+CD127^-Foxp3^+$, and CD8 T cells: $CD3^+CD8^+$ (Williams P, et al ASH 2017 Oral presentation, abstract # 185): see updated data in section 2.6.1. Eight healthy human BMs were used as controls. Blasts and T-cells were evaluated at the same time-point. OX40 and PD-1 positive TILs were significantly higher in untreated AML BM as well as relapsed AML BM as compared to healthy donor BM. AML patients had significantly increased $OX40^+$ TILs as compared to healthy control marrow across all three lymphocyte subsets interrogated including CD4 effector, T regs, and cytotoxic $CD8^+$ cells. Similarly AML patients had significantly increased $PD\text{-}1^+$ TILs as compared to healthy control BMs across these three lymphocyte subsets. Furthermore, $PD\text{-}1^+$ and $OX40^+$ TILs were significantly higher in relapsed AML BM as compared to newly diagnosed untreated AML[15] There was significant variability in BM expression of costimulatory receptors and ligands between individual patients. The expression of costimulatory receptors and ligands differed significantly between BM and PB from the same time-point in the same patient with higher expression in the BM T-cells on most occasions. A larger sample size is needed

to confirm these data and find additional associations, and this is currently underway at our institution.

Thus, clinically targetable checkpoint receptors including PD-1, OX40 and potentially others are overexpressed in the BM of patients with AML. These findings in baseline BM samples from AML patients (especially in relapsed AML) support the proposed clinical trials of OX40 and/or PD-L1 checkpoint blockade with avelumab combinations in AML.

Figure 1: PD-1 expression in AML T-lymphocyte subsets

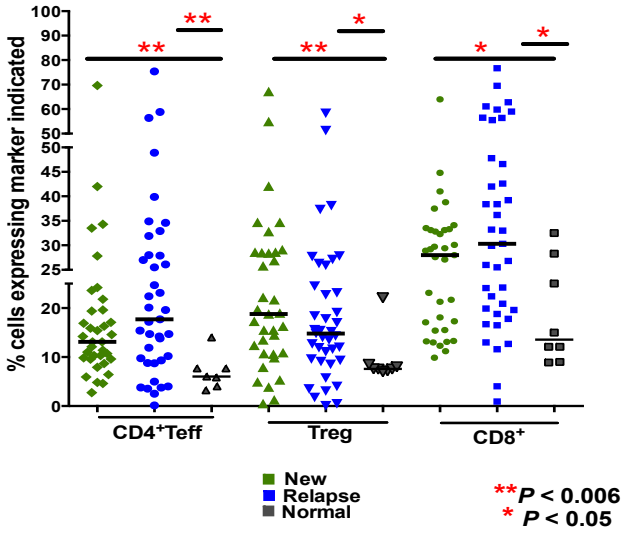
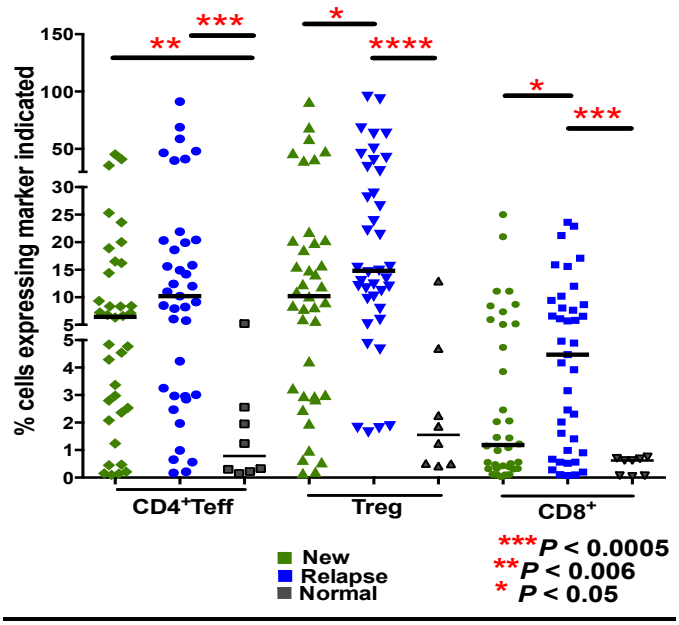


Figure 2: OX40 expression in AML T-lymphocyte subsets



2.2.3 CD33 monoclonal antibodies in AML (GO, Mylotarg)

CD33 is a member of the sialic acid-binding immunoglobulin-like lectins (Siglecs) and is a myeloid differentiation antigen [18] primarily expressed at very early stages on myeloid progenitors. CD33 is highly (>90%) expressed on AML blasts [19]. Conjugated antibodies were engineered with the intention of improving the anti-tumor efficacy of CD33 antibodies by leveraging the endocytolytic property of CD33.

Thus far the largest clinical experience with a monoclonal antibody in AML has been with GO, a humanized CD33-directed antibody drug conjugate (ADC) covalently linked to a semisynthetic derivative of a potent DNA-damaging toxin calicheamicin. In 2000, GO was granted accelerated approval by the United States FDA [20] on the basis of a 30% overall response rate (CR + CRi) in phase II clinical trials [21] in patients with AML in first relapse [22]. Response duration was difficult to determine due to the high prevalence of post-remission therapies, however, responses were relatively short.

However, no difference in OS was observed in the subsequent phase III SWOG S0106 trial designed to meet FDA post-approval requirements [23]. The lack of clear clinical benefit, concerns about increased side effects, and slightly increased early death rate with GO in this SWOG trial [23], led to voluntary withdrawal of the drug from United States markets.

Particular concerns were related to life-threating sinusoidal obstruction syndrome or veno-occlusive disease, which was more likely to occur when the drug was used in higher concentration, in combination with hepatotoxic agents, or within three months of allogeneic stem cell transplant (SCT) (incidence rate 9-14%) [24]. The postulated mechanisms included either dissociation of calicheamicin from the anti-CD33 antibody causing direct toxic effect to hepatocytes or uptake of GO by CD33(+) cells residing in the hepatic sinusoids [25]. The potential benefits of GO in this trial might have been masked due to a suboptimal dosing schema as well as failure to perform patient subgroup analysis.

Subsequently, large randomized trials investigated GO in addition to standard induction chemotherapy in adults with newly diagnosed AML. These studies [26-28] showed statistically improved OS when GO was added to standard induction, particularly in younger patients with intermediate and/or favorable risk cytogenetics,

In older patients, the addition of GO to cytotoxic induction regimens improved the relapse risk, event-free survival and overall survival without improving the response rate or early mortality rate[28,29]. In a meta-analysis of these randomized clinical trials, the addition of GO significantly reduced the risk of relapse (HR 0.8; 95%CI 0.72-0.89, p<0.001), improved relapse free (HR 0.8; 95%CI 0.76-0.94, p=0.001) and overall survival (HR 0.89; 95%CI 0.82-0.97, p=0.01), particularly in patients without adverse cytogenetics [30]. These data led to the reassessment of the role of GO in AML [31,32]. These multiple datasets con- firmed the clinical benefit of GO in patients with AML and led to its FDA approval in September 2017 for the treatment of newly diagnosed or relapsed/ refractory CD33þ AML in adults, and pediatric patients 2 years of age and older.

Currently, clinical trials are ongoing to evaluate the efficacy and toxicity of GO either as a monotherapy or in combination with chemotherapy in frontline (France) and relapsed (United States) patients with AML, including its addition to standard conditioning prior to

ASCT [ClinicalTrials.gov: NCT01869803, NCT02473146, NCT02221310].

The leukemic cell lysis by CD33 directed payload will result in the release of intracellular products that may serve as neoantigens to prime the T-cells. GO is being filed with the FDA for approval in July, 2017 and it is expected that it will be favorably reviewed by the ODAC resulting in re-introduction of GO to the US market. Combination strategies with GO are being developed to further enhance the single-agent response. Inhibition of smoothened hedgehog signaling by cyclopamine induced monocytic differentiation in AML (HL-60) cell lines[33]. The CD33 expression is preserved in cell lines after smoothened inhibition. Furthermore, GO and glasdegib have independent modes of action and non-overlapping toxicities making them suitable for combination approaches.

2.2.4 Hedgehog signaling in AML

The hedgehog (Hh) protein family is a group of secreted intercellular signaling molecules [34]. This pathway plays critical role in proliferation, differentiation and migration of embryonic cells during embryonic development [35-37]. The hedgehog pathway also plays a key role in primitive and adult hematopoesis [38-40] and regulates entry of cells into cell cycle [41], inhibition of apoptosis [42] and maintenance of self-renewal of stem-cells in various tissues [43]. In humans, the Hh family consists of three distinct ligand, Sonic (Shh), Indian (Ihh) and Desert (Dhh). Ihh is found most specifically within hematopoietic cells [39]. In absence of Hh ligand Patched (*Ptch*) suppresses the Hh pathway by inhibiting the activation of Smoothened (*Smo*) – a constitutively activated 7-transmembrane receptor [44-46]. When Hh ligand binds the *Ptch* receptor, the latter is deactivated, resulting in Smoothened (*Smo*) being released into the cytoplasm. Smo can then initiate a signaling cascade that activates members of the Glioma associated oncogene homologs (*Gli*) family of zinc-finger transcription factors. Activated *Gli* translocates to the nucleus and regulates transcription of Hh target genes which act as regulators of cell proliferation, survival and apoptosis [47]. Mutations in genes encoding proteins involved in the Hh pathway such as *Ptch* and *Smo* (ligand independent mechanism) have been reported in basal cell carcinoma, medulloblastoma, and rhabdomyosarcoma [48,49]. In addition to mutations in components of Hh signaling, several cancers have been shown to abnormally express the Hh ligand; including small cell lung cancer, pancreatic, colon, gliomas, multiple myeloma, Chronic Myeloid Leukemia (CML) and B-cell lymphoma [50-53]. Conversely, inhibition of Hedgehog signaling by cyclopamine (a steroid alkaloid that inhibits Hh signaling via *Smo*) can induce significant tumor regression, as demonstrated in human engrafts of medulloblastoma [54], human xenografts of prostate cancer [55] and pancreatic adenocarcinoma cell lines [56]

Ihh and its receptor molecules have been shown to be highly expressed in cord blood CD 34+ stem cells [43]. Hh components *Ptch* and *Smo* are expressed in several leukemic cell lines; including Jurkat cells [57]. Similarly, Shh and *Gli* are expressed in human Promyelocytic leukemia (HL-60) and KG-1 cells. Interestingly, these components were detectable in primary acute leukemic cells, but not acute lymphoblastic cells [58]. Kobune et. al. studied the function of Hh signaling in acute leukemic cells including CD 34+ cells using both reverse transcription-polymerase chain reaction (RT-PCR) for Hh pathway components and a *Gli*- responsive receptor assay [34]. They found that Ihh was expressed in six out of seven leukemic cell lines; except for NB4. Similarly; *Gli1* was detected in six out of seven cell lines and *Gli2* was detected in all seven cell lines. It has been demonstrated that *Gli1* and *Gli2* are the prime transcriptional factors involved and

constitutive activation of at least one of them is of critical importance in cancer development [59-61]. It is known that Ihh contributes to the proliferation of cord blood CD34+ stem progenitor cells [62]. To study the effect of Ihh signaling in leukemic cell lines, CD34+ leukemic stem cells were exposed to chemical inhibitor cyclopamine. They observed a dose-dependent decrease in percent survival of all leukemic cell lines, although no changes were observed on exposure to control compound tomatidine. Thus, Ihh signaling plays an important role in growth and survival of these leukemic cells. Similarly, they were able to show that blockage of Ihh signaling by cyclopamine increased the expression of annexin V+: a marker of apoptosis. Thus, Ihh signaling induces apoptosis in CD34+ leukemic stem cells.

2.3 DRUG INFORMATION

2.3.1 PF-04518600 (OX40 mAb): Drug Information summary

PF-04518600 is a fully human IgG2 agonistic mAb specific for human OX40. PF-04518600 binds with high affinity to human OX40 protein. On human T cells in culture, PF-04518600 promoted T-cell proliferation and cytokine secretion only when T cells were activated and PF-04518600 was plate bound. PF-04518600 binds cynomolgus monkey OX40 with a lower affinity. With high concentration of anti-CD3 activation, similar downstream signaling of monkey OX40 by PF-04518600 was observed, such as activation of NFκB and IL-2 secretion. In addition, a mouse surrogate antibody (OX86 mIgG1) demonstrated anti-tumor activity in a syngeneic CT26 tumor model.

Treatment with a combination of OX86 mIgG1 and a mouse anti-4-1BB IgG1 surrogate antibody further inhibited tumor growth compared to single antibody treatment or an isotype control in the CT26 murine colon carcinoma model. In a less immunogenic B16-F10 murine melanoma model, combination treatment significantly enhanced tumor T-cell infiltration and T-cell proliferation.

After single IV dosing of PF-04518600 to cynomolgus monkeys, mean CL values ranged from 0.003 to 0.009 mL/min/kg, and mean Vss ranged from 0.042 to 0.123 L/kg resulting in mean t½ values ranging from 8 to 15 days. In the repeat-dose toxicity study, there were no apparent sex-related differences in systemic exposure (as assessed by Cmax and AUC168) within a dose group for all dose groups. In addition, mean systemic exposure increased with increasing dose and was higher on Study Day 22 compared to Study Day 1. ADA was detected in all dose groups.

Based on the PK observed in cynomolgus monkeys, the PK of PF-04518600 in humans is expected to have a CL of 1.55 mL/kg/day, a Vc of 31.3 mL/kg, and t½ of approximately 25 days.

In the pivotal 1-month repeat-dose toxicity study in cynomolgus monkeys, no direct organ toxicities were observed as would be expected for a target that is only minimally expressed on a small number of immune cells. Minimal evidence of pharmacology, (increases in proliferating Ki67+, CD4+ and CD8+ effector memory T cells and in HLA-DR+ monocytes) was seen at all dose levels (1-100 mg/kg/week) in the 1-month monkey study and exposure margins ranged from approximately 24-3800-fold (based on AUC) over the proposed clinical starting dose of 0.01 mg/kg. In addition, PF-04518600 was well tolerated at doses up to the highest dose tested, with an NOAEL established at 100 mg/kg, administered weekly by IV injection. At the end of the dosing phase in the 1-month study, Cmax and AUC associated with this dose were 5360 µg/mL and 537000

□g•h/mL, following repeated weekly administration. The exposure margin (based on AUC) at the NOAEL was approximately 3800-fold and was calculated based on estimated human exposures at the proposed starting dose of 0.01 mg/kg in the planned FIP clinical study (B0601002).

No effects on inflammatory cytokines (IL-1, IL-2, IL-4, IL-6, IFN-g, and TNF) were observed in the single dose exploratory monkey study within the first 48 hours postdose. Furthermore, in in vitro cytokine release assays, PF-04518600 did not induce production of IFN-γ, IL-6, or TNF in human whole blood or non-stimulated PBMC's. Based on these data, the overall risk from PF-04518600-induced cytokine release in humans is low. In addition, combination of PF-04518600 and UTOMILUMAB (anti-4-1BB mAb) did not induce cytokine secretion from either non-stimulated or stimulated T cells, which supports further exploration of the combinatorial treatment in patients.

In the first-in-patient study (FIP), Protocol B0601002, PF-04518600 monotherapy (Part A) is being studied in cancers that are considered to be amendable to immunotherapy, including advanced or metastatic hepatocellular carcinoma (HCC), melanoma, clear cell renal cell carcinoma (RCC), and head and neck squamous cell carcinoma (HNSCC). PF-04518600 will also be studied in combination with UTOMILUMAB (anti-4-1BB mAb, see UTOMILUMAB Investigator Brochure) in Protocol B0601002 Part B in patients with advanced or metastatic melanoma, head and neck squamous cell carcinoma (HNSCC), non-small cell lung cancer (NSCLC), bladder, gastric or cervical cancers, who are unresponsive to existing therapies, for whom no standard treatment is available, or who have declined standard therapy. Preliminary clinical data from 9 patients in Part A1 indicate that PF-04518600 is well tolerated.

Overall, the nonclinical package and the preliminary clinical experience with PF-04518600 support the safety and design of Protocol B0601002 for both single agent treatment and in combinations..

For further details on preclinical toxicity and safety, dosage, and clinical information please see the latest version of the PF-04518600 IB attached as Appendix.

2.3.2 Avelumab (PDL1 mAb): Drug information summary

Because of the known role of programmed death ligand 1 (PD-L1) in the suppression of T cell responses and the strong correlation between PD-L1 expression and prognosis in cancer, the blockade of the PD-L1/programmed death 1 (PD-1) interaction presents a highly promising strategy for cancer immunotherapy.

Avelumab (company code: MSB0010718C) binds PD-L1 and blocks the interaction between PD-L1 and PD-1. This removes the suppressive effects of PD-L1 on anti-tumor CD8+ T cells, resulting in the restoration of cytotoxic T cell response.

Physical, chemical, and pharmaceutical properties and formulation

The active pharmaceutical ingredient in avelumab drug product is a fully human antibody (calculated molecular weight of 143832 Dalton) of the immunoglobulin G (IgG) 1 isotype that specifically targets and blocks PD-L1, the ligand for PD-1.

Avelumab drug product is a sterile, clear, and colorless concentrate for solution intended for intravenous (iv) infusion. The drug is presented at a concentration of 20 mg/mL in single-use glass vial containing 200 mg of avelumab.

Avelumab drug product must be stored at 2°C to 8°C until use, and it must not be frozen. Rough shaking of avelumab product must be avoided. Avelumab drug product must be diluted with 0.9% saline solution; alternatively a 0.45% saline solution can be used if needed. It is recommended that the diluted avelumab solution is used immediately.

Nonclinical pharmacology

The nonclinical pharmacology studies have shown that avelumab functionally enhances T cell activation in vitro and significantly inhibits the growth of PD-L1 expressing tumors in vivo.

Avelumab binds to human PD-L1 with a high affinity of 0.7 nM and not to any other B7 family proteins, and competitively blocks the interaction of PD-L1 with PD-1. The in vitro study results have shown that by binding to PD-L1, avelumab effectively enhances T cell activation as measured by interleukin (IL)-2 or interferon-gamma (IFN-g production. In addition, as a fully human IgG1 antibody, avelumab has the potential to trigger the antibody-dependent cell-mediated cytotoxicity (ADCC) against target cells expressing PD-L1.

As a monotherapy, avelumab has demonstrated anti-tumor activity against murine MC38 colon carcinoma tumors that are characterized by a high level of PD-L1 expression. A dose-dependent trend was observed, and 400 µg per dose (20 mg/kg, approximately) was identified as the optimally effective dose when given every third day for 3 total doses.

The in vivo anti-tumor effects were found to be primarily mediated by CD8+ T cells as evidenced by the observation that in vivo depletion of this cell type completely abrogated the anti-tumor efficacy of avelumab. The contribution of ADCC as a potential mechanism of anti-tumor activity was further demonstrated in vivo using a deglycosylated version of avelumab to abrogate fragment crystalline (Fc) receptor binding or via the systemic depletion of natural killer (NK) cells. In both settings, loss of in vivo ADCC potential significantly reduced the anti-tumor activity.

The combination of avelumab with commonly used cancer treatments, such as cytotoxic agents and radiation therapy, resulted in an improved anti-tumor activity. Chemotherapy with combination therapy (with folinic acid, 5-fluorouracil, and oxaliplatin [FOLFOX], and radiation therapy showed the better tumor growth inhibition. In particular, radiation therapy was found to be a highly synergistic combination with avelumab capable of causing complete regression of established tumors probably through generating anti-tumor immune memory.

Various immunomonitoring assays were incorporated into the in vivo studies. Treatment with avelumab resulted in a consistent increase in the percentage of CD8+PD-1+ T cells and an increased frequency of CD8+ T cells with an effector memory (TEM) phenotype as determined by flow cytometry. Furthermore, these changes correlated with the anti-tumor effect. Increases in tumor antigen-specific T cell responses, as measured by enzyme-linked immunosorbent spot and pentamer immunoassays, were evident following treatment with avelumab and these responses were enhanced when combined with FOLFOX or radiation. Hence, increases in CD8+PD-1+ T cells, CD8+ TEM cells, and antigen-specific T cell responses, may be leveraged as pharmacodynamics (PD) biomarkers with translational relevance to the clinical setting.

Nonclinical pharmacokinetics and metabolism

As expected for a monoclonal antibody (MoAb) binding to a cellular target, avelumab demonstrated pronounced non-linear pharmacokinetic (PK) characteristics in mice and monkeys in single dose studies at doses below 20 mg/kg, suggesting a combination of first order catabolic clearance and saturable target-mediated clearance. Toxicokinetic data from repeated dose toxicity studies in mice, rats, and monkeys indicated that the PK of avelumab was linear within the dose range of 20 to 140 mg/kg, suggesting that the target mediated clearance could be saturated when higher doses than 20 mg/kg are administered. Similar terminal half-lives (t1/2) of approximately 60 to 70 hours were observed in toxicity studies in mice and monkeys.

A PK/ PD study in C57BL/6 mice was used to correlate receptor occupancy data of avelumab in blood with drug concentrations. A plasma concentration of 58.5 µg/mL was calculated as required for 95% target occupancy (TO) in this model.

Avelumab is immunogenic in mice, rats, and monkeys with a lower incidence of anti-drug antibodies (ADAs) at higher doses. The latter is probably due to interference of free avelumab with the immunogenicity assay (drug interference). In animals, the generated ADAs seem to have the potential to increase the clearance of the avelumab. As the fully human avelumab represents a foreign protein to the immune system of animals, the observed immunogenicity of avelumab in rodents and non-human primates is not deemed predictive for an immune response to avelumab in humans.

Nonclinical toxicology

The toxicological profile of avelumab was evaluated in repeat-dose toxicity studies of 4-week duration with once weekly IV bolus injection/infusion of avelumab in mice, rats, and cynomolgus monkeys. A repeat-dose toxicity study with intermittent once weekly IV infusion of avelumab over 13 weeks followed by an 8-week recovery period in cynomolgus monkeys was also conducted. In addition, in vitro cytokine release assays (CRA) in human and cynomolgus monkey whole blood and peripheral blood mononuclear cells (PBMCs) followed by an optimized CRA in phytohemagglutinin (PHA) pre-stimulated PBMCs from 16 human volunteers was completed. Tissue cross reactivity (TCR) studies in normal human and cynomolgus monkey tissues have also been was performed.

On the basis of the binding affinity data, the cynomolgus monkey and the mouse were selected as relevant species for the nonclinical safety testing of avelumab. Due to severe hypersensitivity reactions after repeated administration of avelumab in mice and the low binding affinity in rats, rodent species are not considered appropriate for nonclinical safety testing of avelumab and therefore, a single species approach (cynomolgus monkey only) is applied.

In cynomolgus monkeys neither in the pilot 4-week iv repeat-dose toxicity study nor in the pivotal 13-week study, clinical signs of hypersensitivity have been seen after repeated treatment with avelumab at dose levels of 20, 60, and 140 mg/kg, respectively. For the pilot 4-week study as well as for the pivotal 13-week IV repeat-dose toxicity study, a no observed adverse effect level (NOAEL) of 140 mg/kg for systemic toxicity was established.

Initial CRA in human and cynomolgus monkey whole blood and PBMCs revealed no

clear-cut evidence for release of pro-inflammatory cytokines. However, a subsequent, optimized CRA demonstrated evidence of potential cytokine release in PHA pre-stimulated PBMCs.

Clinical safety

Avelumab is currently in clinical development across Phases I, II, and III. The attached updated version of the IB (Appendix) includes safety data from the following 4 clinical trials:

- EMR 100070-001: A Phase I, open-label, multiple ascending dose trial to investigate the safety, tolerability, pharmacokinetics, biological and clinical activity of avelumab in subjects with metastatic or locally advanced solid tumors and expansion to selected indications
- EMR 100070-002: A Phase I trial to investigate the tolerability, safety, pharmacokinetics, biological and clinical activity of avelumab in Japanese subjects with metastatic or locally advanced solid tumors, with expansion part in Asian subjects with gastric cancer
- EMR 100070-003: A Phase II, single arm, open-label, multicenter trial to investigate the clinical activity and safety of avelumab in subjects with Merkel cell carcinoma (MCC)
- EMR 100070-004: A Phase III open-label, multicenter trial of avelumab versus docetaxel in subjects with non-small cell lung cancer that has progressed after a platinum-containing doublet

EMR 100070-001 is a Phase I, open-label, multiple ascending dose trial to investigate the safety, tolerability, PK, biological and clinical activity of avelumab in subjects with metastatic or locally advanced solid tumors and expansion to selected indications. This trial consists of 2 parts. In the dose escalation part, sequential cohorts of subjects were enrolled at progressively higher dose levels (ranging from 1.0, 3.0, 10.0, and 20.0 mg/kg once every 2 weeks) with a 3 + 3 algorithm design for determination of the maximum tolerated dose (MTD) of avelumab; in the treatment expansion phase, subjects in different tumor cohorts are being treated with 10 mg/kg of avelumab once every 2 weeks until, confirmed progression, unacceptable toxicity, or any reason for withdrawal occurs. More than 1500 subjects have been enrolled in the EMR 100070-001 trial. The 3 + 3 dose escalation algorithm to determine the MTD is complete and a dose of 10 mg/kg once every 2 weeks was determined for the tumor expansion cohorts on the basis of safety, PK, and PD observations. The treatment expansion part of the trial consists of 16 tumor treatment cohorts. As of 05 November 2015 (data cutoff for a pre-planned safety data review by the study Safety Monitoring Committee [SMC]), 53 subjects in the dose escalation part had received avelumab (4, 13, 15, and 21 subjects had received 1.0, 3.0, 10.0, and 20.0 mg/kg of avelumab, respectively) and 1300 subjects in the pooled expansion part had received 10 mg/kg avelumab and were followed up for at least 4 weeks.

The safety summary for this Investigator's Brochure summarizes data from 1300 subjects treated in the pooled treatment expansion cohort from the ongoing Phase I Trial EMR 100070-001 (as of 05 November 2015). The pooled data included subjects treated in all tumor expansion cohorts, including non-small cell lung cancer (NSCLC), metastatic gastric cancer, breast cancer, colorectal cancer, castrate-resistant prostate cancer, adrenocortical carcinoma, melanoma, mesothelioma, urothelial carcinoma, ovarian cancer, renal cell carcinoma, and squamous cell cancer of the head and neck. Safety data are also summarized for 52 subjects in the ongoing Phase I Trial EMR 100070-002 and for 88 subjects in the ongoing Phase II Trial EMR 100070-003 (as of 17 December

2015). For Trial EMR 100070-004, an overview of the serious adverse events (SAEs) is provided.

Most of the observed adverse events (AEs) were either in line with those expected in subjects with advanced solid tumors or with class effects of MoAb blocking the PD-1/PD-L1 axis. Infusion-related reactions including drug hypersensitivity reactions and immune-mediated adverse reactions have been identified as important risks for avelumab. Respective risk mitigation measures have been implemented in all ongoing clinical studies with avelumab.

Clinical efficacy

The clinical efficacy information summarized in the IB (appendix) includes data from the NSCLC and ovarian cancer expansion cohorts of the ongoing Phase I Trial EMR 100070-001, and for 20 subjects in the gastric cancer expansion cohort of the ongoing Phase I Trial EMR 100070-002.

The NSCLC expansion cohort in the ongoing Phase I Trial EMR 100070-001 had a cutoff date of 15 January 2015, 6 months after start of avelumab treatment of the last subject in this expansion cohort (a total of 184 treated subjects). The objective response rate (ORR) based on confirmed and unconfirmed responses for subjects treated in the NSCLC expansion cohort was 14.1% (26 of 184 NSCLC subjects). Progression free survival (PFS) and overall survival (OS) were all evaluated for all NSCLC subjects treated in the expansion phase. As of 15 January 2015, the median PFS and OS for the NSCLC treatment expansion cohort were 11.6 weeks and 8.4 months, respectively.

The clinical activity of avelumab was also evaluated by subjects' tumor PD-L1 expression status in the NSCLC expansion cohort. An objective response was observed in 20 of 122 subjects (16.4%) who were PD-L1 positive (defined as having at least 1% PD-L1 positive tumor cells) compared with 2 of 20 subjects (10.0%) who were considered PD-L1 negative (defined as having less than 1% PD-L1 positive tumor cells). A longer median PFS (12.0 vs 5.9 weeks) and OS (8.9 vs 4.6 months) were both observed in PD-L1 positive compared with PD-L1 negative subjects.

The ovarian cancer expansion cohort had a data cutoff of 13 February 2015, approximately 13 weeks after the start of avelumab treatment on the last subject who was included in this pre-planned interim analysis on this expansion cohort. The ORR based on confirmed and unconfirmed responses for subjects treated in the ovarian cancer expansion cohort was 10.7% (8 of 75 subjects). The median PFS for the ovarian cancer expansion cohort was 11.4 weeks (95% confidence interval (CI): 6.3 to 12.0 weeks).

The preliminary efficacy data for the ongoing Phase I Trial EMR 100070-002 are based on a data cutoff of 11 March 2015. As of the data cutoff, 3 of 20 subjects responded to trial treatment (all responses were partial responses [PRs] and all responses were confirmed responses), and the best overall response (BOR) was 15.0% (95% CI: 3.2% to 37.9%). The median PFS of this group was 11.9 weeks (95% CI: 6.0 to 12.3 weeks).

For further details on preclinical toxicity and safety, dosage, and clinical information please see the latest version of the PF-04518600 IB attached as Appendix.

2.3.3 Azacitidine (Vidaza®): Drug Information Summary

Azacitidine, an analog of the pyrimidine nucleoside cytidine, has effects on cell differentiation, gene expression, and deoxyribonucleic acid (DNA) synthesis and metabolism. Since the early 1970s, azacitidine has been investigated primarily in the US for the treatment of acute leukemia. Clinical studies have focused mainly on patients with disease refractory to conventional chemotherapy. Results of these investigations demonstrated activity of azacitidine in the treatment of AML. Clinical studies subsequently evaluated the effects of 5-azacitidine in a variety of other malignant and hematologic disorders, including solid tumors, hemoglobinopathies (e.g., thalassemia and sickle cell anemia), and MDS. In 1984, the Cancer and Leukemia Group B (CALGB) began a series of clinical studies with azacitidine in patients with MDS. These studies, in addition to other supportive data, led to the approval of Vidaza® (azacitidine) in May 2004 for the treatment of MDS.

Azacitidine inhibits the methylation of newly synthesized DNA by inhibiting DNA methyltransferase (DNMT).[66-68] Increased methylation of DNA (hypermethylation) may result in the silencing of critical genes responsible for cell growth control and differentiation. Hypermethylation of CpG islands spanning the promoter regions of tumor suppressor genes is commonly associated with cancers.[69] It is now widely recognized that hypermethylation of DNA is frequently associated with myelodysplastic syndromes and other cancers,[70-72] such as renal,[73] melanoma,[74] breast,[75] colorectal,[76] non-small cell lung[77] and hematologic malignancies.[78] Azacitidine is believed to exert its antineoplastic effects through hypomethylation and cytotoxicity on abnormal hematopoietic cells in the bone marrow.[79-83] Hypomethylation may restore normal function to genes that are critical for differentiation and proliferation.[69,84,85] The cytotoxic effects of azacitidine cause the death of rapidly dividing cells, including cancer cells that are no longer responsive to normal growth control mechanisms.[79,86-88]

The cytotoxicity of azacitidine is proportional to dose and exposure time.[79,80] Although the mechanisms of cytotoxicity are complex and multifaceted, there is general agreement that incorporation of azacitidine into DNA and ribonucleic acid (RNA), and inhibition of protein synthesis, are critically important.[89] Cytotoxicity is greatest in cells that are proliferating (S phase) and metabolically active.[79] Cytotoxic effects may also be mediated through induction of the DNA damage response pathways.[88] Nonproliferating cells are relatively insensitive to azacitidine.[79]

Toxicology studies have been conducted in mice, rats, dogs, and Rhesus monkeys.[90] Most of the studies were performed during the 1970s and early 1980s according to existing guidelines and standards in place during that period. The preclinical studies identified the bone marrow, liver, kidneys, and lymphoid tissues (spleen, lymph nodes, and thymus) as the main target organs of toxicity for azacitidine.[90] In single-dose studies, the lethal dose of azacitidine after intravenous (IV) administration in mice, rats, and dogs was approximately 250 mg/m^2. Repeated daily dosing appears to increase the toxicity of 5-azacitidine.[90] The genotoxicity of azacitidine is consistent with that of other nucleoside analogs that interact with nucleic acids.[90] Likewise, similar to other agents with cytostatic properties, azacitidine was embryotoxic and reduced the reproductive performance in mice and rats.[90]

Limited azacitidine pharmacokinetic data are currently available. Based on human plasma concentrations of total radioactivity (which represents parent drug plus circulating metabolites), azacitidine is rapidly absorbed when given subcutaneously

(SC), with maximum plasma concentrations found 0.5 to 2 hours after dosing.[90] Azacitidine and/or its by-products are then rapidly cleared by the kidneys. The half-lives and percent radioactivity recovered in urine are similar following IV and SC routes of administration. The effects of renal or hepatic impairment, gender, age, or race on the pharmacokinetics of azacitidine have not been studied.[90] A single dose (75 mg/m^2) SC versus IV crossover study in 6 MDS subjects[91] revealed an approximate bioavailability of 89% for the SC dose (range 52% to 128%) with mean half-lives of 0.69 hour and 0.36 hour after SC and IV administration, respectively. These results demonstrated that azacitidine is rapidly and nearly completely absorbed after SC administration and that elimination is also rapid. The apparent SC clearance (167 L/h or 2791 mL/min) and systemic IV clearance (147 L/h) of azacitidine exceeded the glomerular filtration rate (approximately 125 mL/min) and total renal blood flow (1200 mL/min) in healthy subjects. This indicates that non-renal elimination (e.g., metabolism, hydrolysis, and/or degradation) plays a role in the elimination of parent azacitidine. In addition, azacitidine 75 mg/m^2 was generally well-tolerated after single SC injection or IV infusion over 10 minutes.[91]

A number of studies have looked at different parenteral doses and schedules of azacitidine, finding maximum tolerated doses of up to 500 mg/m^2 when administered weekly.[92]

During the two decades between the start of the CALGB studies and the approval of azacitidine, a new understanding of MDS has developed, such as the World Health Organization (WHO) diagnostic criteria, the International Prognostic Scoring System (IPSS), and the International Working Group (IWG) response criteria. Silverman et al. reevaluated the combined data (N = 309) from 3 of the CALGB studies using the WHO classification system for MDS and AML and the IWG response criteria.[93] Using the IWG response criteria in MDS patients, response rates were between 40% and 70% in azacitidine treated patients. Ten to 17% of patients achieved a complete remission; partial remission was rare; and 23% to 36% of patients had a hematologic improvement. In patients with AML (N = 103), 35% to 48% had hematologic improvement or better responses. The median survival time for 27 patients assigned to azacitidine was 19.3 months compared with 12.9 months for the 25 patients assigned to observation.[93]

A randomized international Phase III trial (Study azacitidine PH GL 2003 CL 001) for higher-risk MDS patients, classified by FAB as RAEB, RAEB-T, or CMML with 0-29% marrow blasts, with an IPSS of Intermediate -2 or High by central pathology/cytogenetic review was recently reported.[94] Patients were randomized to azacitidine (75 mg/m^2/day x 7days in 28 day cycles) or conventional care regimens (CCR), where CCR was pre-selected by the Investigator as best supportive care (transfusions, antibiotics, and G-CSF for neutropenic infection), low-dose cytarabine (20 mg/m^2/day x 14 days in 28 day cycles); or standard chemotherapy (conventional induction/consolidation). Patients were stratified by FAB/IPSS and randomized 1:1 to azacitidine or CCR. This trial did not allow erythropoietin. Three hundred fifty eight patients (70% male) were randomized at 79 centers to azacitidine (N=179) or CCR (N=179): best supportive care only (N=105, 59%), low-dose cytarabine (N=49, 27%), or standard chemotherapy (N=25, 14%). Median age was 69 years (range 38-88 years). The azacitidine and CCR groups were comparable for baseline patient characteristics. At baseline, 95% of patients were higher risk: RAEB (58%), RAEB-T/WHO AML (34%), CMML (3%), and other (5%). By IPSS, 87% were higher risk: Intermediate -2 (40%), High (47%), and 13% Indeterminate/other. Azacitidine was administered for a median of 9 cycles; low-dose cytarabine for 4 cycles.

Median follow-up for the survival analysis was 21.1 months. Azacitidine demonstrated statistically superior overall survival compared to CCR, with a median overall survival of 24.4 months vs. 15 months for CCR (stratified log-rank p=0.0001, hazard ration 0.58). Two-year survival approximately doubled in the azacitidine arms compared to CCR: 51% vs. 26% (p<0.0001). Azacitidine was well tolerated with safety data consistent with previous reports.

Further details can be found in the azacitidine drug information (**Appendix**), which contains comprehensive pharmacology, toxicology, pharmacokinetics, pharmacodynamics, metabolism, preclinical, and clinical efficacy and safety data information.

2.3.4 Gemtuzumab Ozogamicin (Mylotarg®, CD33 mAb): Drug Information Summary

Please see the updated GO INVESTIGATOR BROCHURE 2016 (**Appendix**), which contains comprehensive pharmacology, toxicology, pharmacokinetics, pharmacodynamics, metabolism, preclinical, and clinical efficacy and safety data information.

2.3.5 Glasdegib: Drug Information Summary

PF-04449913 (Glasdegib) is a potent and selective inhibitor of Hedgehog (Hh) signaling in vitro and has demonstrated significant antitumor efficacy in vivo. In a mouse model of Hh pathway-driven tumor (medulloblastoma), glasdegib inhibits pathway activation(Gli1 expression) and produces rapid and complete tumor regression. Glasdegib also reduced leukemic burden in a blast crisis chronic myeloid leukemia mouse model, and inhibited tumor formation in secondary recipients. Preclinical pharmacokinetic/ pharmacodynamic (PK/PD) modeling suggests a target human dose of 15 mg/day is projected to yield at least 50% of tumor Gli1 mRNA inhibition from baseline levels.

Absolute oral bioavailability of glasdegib following single dose oral administration was 33% in rats and 68% in dogs. Plasma protein binding of glasdegib in mouse, rat, dog, and human plasma ranged from 85% to 93%. After repeat dose administration in rats and dogs, glasdegib Cmax and AUC24 values increased in a greater than dose-proportional manner with no sex differences in drug exposure. Following oral administration of [14C]glasdegib to pigmented rats, distribution of [14C]glasdegib-derived radioequivalents was widespread in most tissues with no quantifiable levels of radioequivalents detected after 8 hours in most tissues, except in the uveal tract and the eye.

The in vitro metabolic profiles of glasdegib was consistent across evaluated preclinical species and humans; all metabolites observed in human in vitro incubations were present in one or more of the evaluated preclinical species. Glasdegib appeared to be metabolized to several oxidative metabolites in vitro as well as in vivo. In vitro, CYP3A is the predominant enzyme mediating the oxidative metabolism of glasdegib. An N-glucuronide conjugate of glasdegib was also identified in the plasma and urine of human subjects following single dose administration of [14C]glasdegib. In vitro, UGT1A9 mediates the formation of this N-glucuronide.

In vitro, glasdegib has a low risk to inhibit and/or induce various evaluated CYP and UGT enzymes and drug transporters at clinically relevant concentrations, but may have the potential to inhibit MATE1 and MATE2K.

Glasdegib was evaluated in rat and dog repeat dose toxicity studies up to 3-month in duration. Glasdegib was well tolerated up to 100 mg/kg/day in the rat and 10 mg/kg/day in the dog. In both the rat and dog, a non-proportional increase in exposure occurred with increasing dose. Deaths and/or moribund euthanasia occurred in the 10-day rat and 1-month dog studies at 500 or 30/15 mg/kg/day, respectively. Cause of death/morbidity in both species was attributed to kidney toxicity. The target organs in the rat included kidney (tubular degeneration/necrosis, cytomegaly, inflammation, regeneration), bone (decreased/disorganized chondrocytes in epiphysis), tooth (degeneration/necrosis/absence of the apical portion) and peripheral nerve (axonal degeneration); the NOAEL was 10 mg/kg/day in the 3-month rat study, corresponding to <1x the projected human Cavg(ss) at steady state. In the 1-month rat study, the kidney changes showed signs of reversibility but did not entirely reverse, while the bone changes persisted. Reversibility of the tooth and peripheral nerve changes could not be evaluated as these changes were present only in the 3-month rat study, which did not include a recovery period.

The target organs in the 3-month toxicity study in the dog were the kidney (tubular necrosis, granular/mineralized casts, dilated tubules) and liver (mild mixed cell inflammation, Kupffer cell pigment accumulation); the NOAEL was 1 mg/kg/day in the 3-month dog study, corresponding to <1x the projected human Cavg(ss) at steady state. In the 1-month dog study, the kidney changes were completely reversed in males and partially reversed in females after a 6-week reversal period. Reversibility of the liver changes could not be evaluated as the changes were present only in the 3-month dog study, which did not include a recovery period.

In the acute CNS and respiratory studies in the rat no effects were observed at the high dose of 50 mg/kg (6x above the projected human efficacious Cmax at steady state). Increases in QT, QTc75 were noted after single doses of >5 mg/kg to dogs which is >4.2x above the projected human efficacious Cmax at steady state. Glasdegib was negative in the definitive in the in vitro bacterial mutagenicity assay, human lymphocyte assay and the in vivo rat micronucleus. The molar extinction coefficient for glasdegib at 290 nm is 9,622 L/mol/cm; therefore, glasdegib has the potential to be phototoxic.

Clinical studies in healthy subjects:
As of 15 July 2015, 4 healthy volunteer studies have been completed (B1371009, B1371010,
B1371014, and B1371015).

1. B1371009: A Phase 1 single-dose study in healthy subjects to evaluate the mass balance and pharmacokinetics of glasdegib. Six (6) healthy male subjects were dosed. This study has completed.

2. B1371010: A Phase 1 2-sequence, 3-period, 3-treatment, single-dose crossover study in healthy subjects to evaluate the effect of food and CYP3A4 inhibition by ketoconazole on single- dose plasma pharmacokinetic. Fourteen (14) healthy male subjects were dosed. This study has completed.

3. B1371014: A Phase 1 study in healthy subjects to estimate the bioavailability of two new glasdegib formulations relative to the current formulation and to evaluate the potential effect of food and a proton-pump inhibitor on glasdegib plasma

pharmacokinetics. Thirty five (35) healthy male subjects were dosed. This study has completed.

4. B1371015: A Phase 1 fixed sequence study in healthy subjects to investigate the effect of multiple doses of the strong enzyme inducer rifampin on glasdegib pharmacokinetics. Twelve (12) healthy male subjects were dosed. This study has completed.
In all clinical studies in healthy volunteers a total of 38 treatment-related TEAEs were reported; all were mild or moderate in severity.

Clinical studies in patients:
As of 15 July 2015, 6 clinical studies have been conducted in cancer patients. Two (2) studies in cancer patients have completed (B1371001, B1371002), and 4 studies are ongoing (B1371003, B1371005, B1371012, and B1371013).

1. B1371001: A Phase 1 dose-escalation, single-agent study in patients with select advanced hematologic malignancies. Forty-seven patients were dosed. This study has completed.

2. B1371002: A Phase 1 dose-escalation, single-agent study in patients with advanced solid tumors. Twenty-three patients were dosed. This study has completed.

3. B1371003: A Phase 1b/2 study of glasdegib in combination with low-dose cytarabine (Ara-C), decitabine, or intensive chemotherapy (cytarabine/daunorubicin), in patients with acute myeloid leukemia or high-risk myelodysplastic syndrome. Two-hundred nineteen (219) patients have been enrolled and treated in this study.

4. B1371005: A Phase 1 dose-finding study of single-agent glasdegib in Japanese patients with select advanced hematologic malignancies, or glasdegib in combination with intensive chemotherapy (cytarabine and daunorubicin) or low-dose cytarabine (LDAC) in patients with previously untreated AML or high-risk MDS. Thirteen (13) patients have been enrolled and treated in this study.

5. B1371012: A Phase 1b/2 study of glasdegib in combination with azacitidine versus placebo in patients with previously untreated Intermediate-2 or High-Risk MDS, AML with 20% to 30% blasts and multi-lineage dysplasia, and CMML. Six (6) patients have been enrolled and treated in this ongoing study.

6. B1371013: A Phase 2 study of single-agent glasdegib versus placebo in patients with primary or secondary myelofibrosis who have been previously treated with a Janus kinase inhibitor. Eleven (11) patients have been enrolled and treated in this ongoing study.

Study B1371001 was a first-in-patient Phase 1 trial with a 3+3 dose escalation design in patients with refractory, resistant or intolerant select advanced hematologic malignancies. Patients received single agent glasdegib orally once daily (QD) continuously in 28 day cycles. Ten dose levels were evaluated in this study, ranging from 5 mg QD to 600 mg QD. The median age was 69 years (range 25-89 years). Other patient characteristics are detailed in the IB. The safety profile appeared favorable with the most common treatment-related AEs being Grades 1/2. The most frequently reported treatment-related AE was dysgeusia (27.7%). Two (2) patients developed dose

limiting toxicities (DLTs) during Cycle 1. One (1) patient dosed at the 80 mg QD dose level with AML that evolved from chronic myelomonocytic leukemia (CMML) developed DLTs of Grade 3 hypoxia and pleural effusion. This patient had an underlying pneumonia prior to coming on study. A second patient dosed at 600 mg QD developed a DLT of edema of inferior limbs. Regarding the MTD determination, changes in QTc values from baseline were seen in some patients, with some pronounced increases at the highest dose levels. Because of this observation, only 5/6 patients were enrolled at the 600 mg dose level and the next lower dose was expanded successfully to 6 patients. The MTD was subsequently determined to be 400 mg QD. The recommended Phase 2 dose (RP2D) in patients with select advanced hematologic malignancies was determined to be </=200 mg QD by comparing the tolerability, PK, and pharmacodynamic profile of glasdegib at doses ranging from 5 to 600 mg QD.

In Study B1371001, PK data indicate that glasdegib is absorbed following oral dosing with a median Tmax of 1- 4 hours after single and multiple dose administration. Following attainment of Cmax, glasdegib plasma concentrations showed a bi-exponential decline with a mean terminal half-life ranging from 17.4 to 34.3 hours. Following repeated daily dosing, glasdegib steady state was achieved by Day 8 and showed a median drug accumulation ratio ranging from 1.2 to 2.5, which is consistent with the estimated half-life. The geometric mean for the percentage of administered dose excreted unchanged in the urine over the dosing interval of 24 hours ranged from 5.89% to 16.8%.

Study B1371002 had a similar 3+3 dose escalation design in patients with select advanced/metastatic solid tumors. The starting dose of glasdegib in this study was 80 mg QD and additional dose levels of 160 mg QD, 320 mg QD and 640 mg QD were evaluated. Twenty three (23) patients were enrolled. Two (2) patients dosed at 640 mg QD developed DLTs during Cycle 1. One (1) patient developed DLTs of Grade 3 nausea, vomiting, and dehydration that persisted despite optimal supportive care. A second patient developed a DLT of inability to administer 80% of the planned dose of glasdegib during Cycle 1 due to glasdegib related Grade 2 fatigue, dehydration, and dizziness, and Grade 1 dyspepsia and dysgeusia. Therefore, the protocol-defined MTD of glasdegib in patients with advanced solid tumors was 320 mg QD. The most frequently reported treatment-related AEs of any grade were dysgeusia (65.2%), fatigue (52.2%), nausea and decreased appetite (34.8% each), dizziness (30.4%), diarrhea and dehydration (26.1% each), vomiting muscle spasms, and alopecia (21.7% each).

In study B1371002, following repeated daily dosing, steady-state was achieved by Cycle 1/Day 8 based on comparison of Ctrough values across PK days in Cycle 1. Following multiple dosing, glasdegib was absorbed with a median time to first occurrence of Cmax (Tmax) of 1-4 hours. The mean terminal plasma half-life (t½) for glasdegib ranged from 17.7 to 20.7 hours. glasdegib accumulated following repeated dosing with a median Rac ranging from 1.35 to 1.75 which was consistent with the observed t½.

Study B1371003 is a Phase 1B/2, open-label, multicenter safety and efficacy study of glasdegib in combination with low dose Ara-C, decitabine, or intensive chemotherapy in patients with acute myeloid leukemia or high-risk myelodysplastic syndrome. For each Ph1B arm separately, a 3+3 dose escalation design in 3-6 patient cohorts was employed to determine the MTD of glasdegib in combination with each standard therapy. The starting dose of glasdegib is 100 mg QD administered orally in 28-day (+/- 4 days) cycles on a continuous basis. Fifty two (52) patients were enrolled in Phase 1B portion of the

study (23 patients treated with glasdegib plus low dose Ara-C [Arm A], 7 patients treated with glasdegib plus decitabine [Arm B], and 22 patients treated with glasdegib plus cytarabine/daunorubicin.

Of the 52 patients treated with glasdegib in Phase 1b, 1 patient in Arm C reported a DLT of polyneuropathy (Grade 4 SAE) on Study Day 18 , which resolved on Day 34. The most frequently reported treatment-related AEs in patients who received glasdegib 100 mg +LDAC (Phase 1b Arm A) were nausea (n = 6, 35.3%), diarrhea and neutropenia (n = 5, 29.4% each), and muscle spasms and dysgeusia (n = 4, 23.5% each). The most frequently reported treatment-related AEs in patients, who received glasdegib 100 mg + decitabine (Phase 1b, Arm B) of any grade were nausea (n=3, 75%), diarrhea, thrombocytopenia, and neutropenia (n=2, 50% each). The most frequently reported treatment-related AEs in patients who received glasdegib 100 mg + cytarabine + daunorubicin of any grade were nausea (n = 13, 81.3%), diarrhea, febrile neutropenia and muscle spasms (n = 7, 43.8% each), dysgeusia (n = 6, 37.5%), stomatitis, headache, fatigue and pyrexia (n = 5, 31.3% each), constipation, dyspepsia, vomiting, anemia, neutropenia, white blood cell count decreased, hypocalcaemia, hypokalemia and alopecia (n = 4, 25% each).

For the Phase 2 portion of the B1371003 study, glasdegib 100 mg QD was selected as the RP2D based on the observed tolerability profile for the combination with LDAC or intensive chemotherapy, and the increase in glasdegib exposures observed with a strong CYP3A4 inhibitor such as ketoconazole (and potential with other azoles/CYP3A4 inhibitors). Phase 2 consists of 2 components: Phase 2 randomized component in unfit patients (P2 Unfit) enrolled to receive either LDAC in combination with glasdegib or LDAC alone, and Phase 2 single arm component in fit patients (P2 Fit) who received glasdegib in combination with cytarabine/daunorubicin. As of the data cutoff date, data were available for 98 patients in the P2 Unfit randomized portion of the study, and 69 patients in the P2 Fit arm. The median age was 70.0 years (range 27-85).

Study B1371005 is an open-label, multi-center, Phase 1B study designed to evaluate the safety, tolerability, PK, PD, and preliminary signs of efficacy of glasdegib administered orally as a single agent in Japanese patients with select advanced hematologic malignancies, or in combination with intensive chemotherapy (cytarabine and daunorubicin) or low-dose cytarabine (LDAC) in patients with previously untreated AML or high-risk MDS.

Study B1371012 is a multi-center, randomized (1:1), double-blind, placebo-controlled Phase1B/2 study to compare the safety, efficacy, PK, and PD of glasdegib or placebo when combined with azacitidine in patients with previously untreated Intermediate-2 or High-Risk MDS, AML with 20-30% blasts and multi-lineage dysplasia, and CMML.

Study B1371013 is a Phase 2, randomised, double-blind, 2-arm study of oral single agent glasdegib versus placebo in a continuous daily regimen of 28-day cycles (+/- 4 days), with defined best supportive therapy allowed in both arms in symptomatic primary or secondary myelofibrosis (MF) patients with a spleen palpable >/=5 cm below the LCM who have previously been treated with >/=1 licensed or experimental JAK inhibitors (JAKi).

As of 01 September 2015, 126 treatment-related SAEs were reported in 64 patients. The most frequently reported treatment-related SAEs (≥2 events) included febrile

neutropenia (15 events), pneumonia (6 events), anemia, fatigue and gastrointestinal hemorrhage (4 events each), nausea, vomiting, device related infection, sepsis, acute kidney injury, acute myocardial infarction and pyrexia (3 events each), abdominal pain, death, edema peripheral, Clostridium difficile infection, dehydration, hyponatremia, presyncope, bacteremia, neutropenia, syncope and electrocardiogram QT prolonged (2 events each).

As of 01 September 2015, 56 deaths were reported in clinical studies of glasdegib. The most frequently reported cause of death was disease progression. Three (3) deaths (1 in Study B1371001 and 2 in Study B1371003) were considered related to study treatment (narratives included in the Section 6.2.4). One (1) additional treatment related death occurred on Study B1371003 (narrative is included in the Section 6.2.4) although this event was not listed as death in the Safety Database at the time of the data cutoff.

In summary, glasdegib appears to be clinically manageable and generally well tolerated in all types of diseases studied to date. Several patients with aggressive hematologic malignancies remained on single agent glasdegib for a prolonged duration.

Further details can be found in the glasdegib information (**Appendix**), which contains comprehensive pharmacology, toxicology, pharmacokinetics, pharmacodynamics, metabolism, preclinical, and clinical efficacy and safety data information.

2.3.6 Venetoclax Drug Information Summary

See the Venetoclax Prescribing Label (Appendix) for additional details on nonclinical and clinical studies.

Bcl-2 overexpression has been implicated in maintaining the survival of AML cells and has been associated with resistance to chemotherapy and inferior overall survival [95]. Venetoclax (VEN) is a potent and selective small-molecule inhibitor of Bcl-2 that has demonstrated cell-killing activity against a variety of leukemia cell lines, primary patient samples and leukemia stem/progenitor cells [96,97]. VEN also has been found to synergize with agents known to down-regulate Mcl-1, including azacitidine. [98]

Based on the mechanism of action and nonclinical and clinical data available to date, the safety profile of venetoclax is well described. The most common adverse drug reactions across all indications are nausea, diarrhea, hematological effects, and serious and/or opportunistic infections. Hematologic effects include neutropenia/febrile neutropenia, thrombocytopenia, anemia, and lymphopenia. Upper respiratory tract infections are among the most common infections. TLS is an important identified risk and is predominantly seen in the CLL population with high tumor burden. Based on pre-clinical data, decreased spermatogenesis has been identified as a potential risk for venetoclax.

Summary of Venetoclax Nonclinical Pharmacology

Venetoclax is a potent, selective and orally bioavailable small molecule inhibitor of Bcl-2 that binds with > 1,000-fold higher affinity for Bcl-2 (dissociation constant [K_i] < 0.010 nM) than for Bcl-X_L (K_i - 48 nM or Mcl-1 (K_i > 444 nM).[96] In vitro, venetoclax has demonstrated cell killing activity against patient-derived chronic lymphocytic leukemia (CLL) cells and a variety of lymphoma and leukemia cell lines[96]. Venetoclax has demonstrated potent killing of AML cell lines, primary patient samples, and leukemic stem/progenitor cells ex vivo, and has also exhibited anti-tumor efficacy in vivo, inhibiting the growth of AML cells systemically engrafted into immunocompromised mice.

Summary of Venetoclax Nonclinical Pharmacokinetics

The pharmacokinetics of venetoclax was evaluated in mice, rats, monkeys, and dogs. Venetoclax pharmacokinetic (PK) profile was characterized by low plasma clearance and low to moderate volumes of distribution. Half-lives ranged from 2.2 hours in monkeys to 12 hours in dogs.

Venetoclax demonstrated high protein binding to human, rat, dog, and monkey plasma proteins (> 99.9%). Blood to plasma ratios showed that venetoclax does not partition preferentially into the red blood cells. Following oral administration of venetoclax to nonclinical species and humans, parent compound and metabolites were mainly cleared via biliary excretion and fecal elimination, with minimal renal clearance.

Venetoclax is predominantly metabolized by cytochrome P450 (CYP) 3A4 (CYP3A4) in vitro; UDP-glucuronosyltransferases (UGTs) are not involved in the metabolism of venetoclax. In addition, venetoclax is also a substrate for P-gp and BCRP. Active uptake of venetoclax was not observed in cells overexpressing OATP1B1, OATP1B3 or OCT1. In vitro studies indicated that venetoclax is not an inhibitor or inducer of CYP1A2, CYP2B6, CYP2C19, CYP2D6, or CYP3A4 at clinically relevant concentrations. Venetoclax is a weak inhibitor of CYP2C8, CYP2C9, and UGT1A1 in vitro, but it is not predicted to cause clinically relevant inhibition due to high plasma protein binding. Venetoclax is a P-gp and BCRP inhibitor and weak OATP1B1 inhibitor in vitro. In vitro, venetoclax is metabolized by CYP3A4 and is a moderate inhibitor of CYP2C8. Definitive in vitro experiments showed that venetoclax is not predicted to be an inducer or inhibitor of the metabolism of CYP2C9 substrate compounds. Venetoclax is not a reversible inhibitor of CYP1A2, CYP2B6, CYP2D6, CYP2C19 or CYP3A4 (IC_{50} > 30 μM) in vitro and does not induce CYP3A4 or CYP1A2 at concentrations up to 10 μM.

Summary of Nonclinical Toxicology

Venetoclax has been assessed in repeated-dose general toxicology studies and in genetic, developmental/reproductive, and safety pharmacology studies. The primary toxicities associated with venetoclax administration included effects on the hematologic system (decreased lymphocytes and erythrocytes) in mice and dogs, the male dog reproductive system (testicular germ cell depletion), and embryo-fetal toxicity in mice.

Summary of Venetoclax Clinical Data

Clinical Efficacy Data for Venetoclax: Preliminary efficacy results are available for subjects with a variety of hematological neoplasms; the drug is approved for the treatment of CLL patients whose cells have a 17p chromosomal deletion. Preliminary data indicate that venetoclax shows promising efficacy in AML.

- In Study M14-212 the ORR for subjects treated with venetoclax monotherapy was 19%.[99]
- In Study M14-358 the ORR for AML subjects (given venetoclax plus azacitidine or decitabine) was 68%.[100]
- In Study M14-387 the ORR for AML subjects (given venetoclax plus low dose ara-C) was 75%.[101]

Venetoclax Clinical Pharmacology and Pharmacokinetics: Venetoclax clinical pharmacology is being evaluated in several Phase I to III clinical trials, and data are available from three Phase I studies (M12-175, M13-367, M12-630), four Phase Ib

studies (M13-365, M12-901, GO29440, GP28331), one Phase II study (M14-212) and five dedicated clinical pharmacology studies (Study M13-364, M14-497, M13-363, M14-253 and M15-101).

In the Phase 1 Study M14-358, preliminary pharmacokinetic results in 31 treatment-naïve AML subjects were available for venetoclax doses ranging from 400 mg to 800 mg when given in combination with decitabine (Arm A) or azacitidine (Arm B) and with or without posaconazole (Arm C). For Arm A and Arm B, venetoclax steady-state mean Cmax and AUC24 (Cycle 2 Day 5) ranged from 1.77 – 3.36 µg/mL and 24.7 – 59.5 µg/mL, respectively. Based on the limited preliminary pharmacokinetic data, there was no evidence to suggest a marked effect of the co-administration of decitabine and azacitidine on the pharmacokinetics of venetoclax. In Arm C of this study, preliminary pharmacokinetic results from 6 subjects were available on Cycle 1 Day 20 (venetoclax 400 mg alone QD until Day 20) and Cycle 1 Day 28 (venetoclax 100 mg QD with posaconazole given from Day 21 to Day 28). Venetoclax Cmax and AUC following co-administration of venetoclax 100 mg with posaconazole were 2.1- and 2.7-fold higher respectively, compared to venetoclax 400 mg alone.

Preliminary pharmacokinetic results of venetoclax are available from 12 treatment-naïve subjects with AML in Cohorts 1 (600 mg) and 2 (800 mg) from the ongoing Phase 1 combination study of venetoclax and low dose cytarabine (Study M14-387). On Cycle 1 Day 10 (with cytarabine), venetoclax mean Cmax and AUC24 values ranged from 2.25 – 2.56 µg/mL and 34.7 – 44.6 µg•hr/mL, respectively. On Cycle 1 Day 18 (venetoclax alone), mean Cmax and AUC values of venetoclax ranged from 2.38 – 2.89 µg/mL and 37.9 – 45.3 µg•hr /mL. Dose-normalized Cmax and AUC24 of venetoclax on Cycle 1 Day 10 (with cytarabine) were comparable to dose normalized Cmax and AUC24 on Cycle 1 Day 18 (venetoclax alone), suggesting that co-administration of cytarabine did not markedly affect venetoclax exposures.

Clinical Safety Data for Venetoclax: As of 05 June 2017, three Phase 1/2 studies have been conducted in the AML indication as described below.

Overview of Phase 2 Study M14-212: Venetoclax Monotherapy in AML
This is a completed study with single agent venetoclax in subjects with R/R AML and those unfit for intensive therapy. A total of 32 subjects were dosed. Exposure, safety, and efficacy data are available for this study.[99] The most common adverse events observed in ≥ 30% of the subjects in Study M14-212 were nausea (59.4%); diarrhea (56.3%); hypokalemia, vomiting (40.6% each); fatigue, headache (34.4% each); hypomagnesemia (37.5%); febrile neutropenia (31.3%); abdominal pain, cough, hypophosphatemia (28.1% each); epistaxis, hyperphosphatemia, hypocalcemia, malignant neoplasm progression (25.0% each); dyspnea, hypotension, peripheral edema, pyrexia, and pneumonia (21.9% each). Serious adverse events were reported in 27 subjects (84.4%), the most common being febrile neutropenia (28.1%), malignant neoplasm progression (25.0%), and pneumonia (15.6%). Three serious adverse events were considered to have a reasonable possibility of being related to venetoclax (i.e., 1 event each of diarrhea, febrile neutropenia, and pseudomonal bacteremia). No cases of TLS occurred during venetoclax treatment.

In this phase II multicenter trial single agent VEN produced an overall response in 5/32 relapsed/refractory AML patients (CR in 1 patient, CRi in 4 patients) [102]. Of the 5 patients with CR/CRi, 3 had *IDH* mutations suggesting that patients with *IDH* mutations may be

particularly sensitive to VEN.

Two ongoing trials are evaluating VEN combination regimens in treatment naïve patients with AML who are ≥65 years of age and who are not eligible for standard induction: (a) to evaluate the efficacy and tolerability of the combination of VEN with a methyltransferase inhibitor (azacytidine or decitabine) (ClinicalTrials.gov Identifier: NCT02203773); (b) to evaluate VEN with low-dose cytarabine (ClinicalTrials.gov Identifier: NCT02287233).

Overview of Ongoing Phase 1b Study (M14-358): Venetoclax in Combination with HMA in Treatment Naïve AML

As of 09 March 2016, a total of 45 subjects ≥ 65 years of age with treatment naïve AML ineligible to receive standard induction therapy were enrolled into the escalation stage at 3 dose levels of venetoclax at 400 mg, 800 mg, and 1200 mg. Venetoclax was administered daily during the 28-day cycles in combination with decitabine (20 mg/m^2 intravenously on Days 1 – 5 once every 28 days) or azacitidine (75 mg/m^2 intravenously or subcutaneously on Days 1 – 7 once every 28 days). Preliminary safety and efficacy data are available from the ongoing dose escalation stage of this trial.[101,103]

The most common adverse events for all subjects in Study M14-358 were nausea (53.3%), diarrhea (44.4%), febrile neutropenia (40.0%), neutrophil count decreased (31.1%), platelet count decreased, cough, and fatigue (28.9% each), edema peripheral and hypokalemia (26.7% each). Events grade 3 and above were reported for the majority (91.1%) of subjects; the most common event was febrile neutropenia (40.0%). Serious adverse events were reported for 27 (60.0%) subjects, including febrile neutropenia (11 subjects), malignant neoplasm progression (3 subjects) atrial fibrillation, abdominal pain, non-cardiac chest pain, pyrexia, pneumonia, sepsis, bone pain (2 subjects each). All other events occurred in 1 subject each. The combination of venetoclax with decitabine and azacitidine demonstrates a tolerable safety profile.

As of 09 March 2016, the ORR, as assessed by the investigators for the subjects enrolled into the 3 dose levels, was 62.2% (28 of 45), with CR in 12 (26.7%), CRi in 15 (33.3%), and PR in 1 (2.2%). Four subjects (8.9%) were reported to have morphologic leukemia-free state (less than 5% blasts in bone marrow aspirate sample with at least 200 nucleated cells) after completion of Cycle 1. Eight patients (17.8%) had resistant disease. However, all of the patients with resistant disease had evidence of blast reduction at completion of Cycle 1. The patients enrolled into the 1200 mg dose level had a shorter follow-up at the time of this analysis.

The maximum tolerated dose has not been reached in either arm and dose escalation stage has completed enrollment. Enrollment into safety expansion at 400 mg and 800 mg dose of venetoclax in combination with both HMAs is ongoing.

Study M14-387: Study M14-387 titled, "A Phase 1/2 study of venetoclax in combination with low-dose cytarabine in treatment naïve subjects with acute myeloid leukemia who are ≥ 65 years of age and who are not eligible for standard anthracycline-based induction therapy," is an ongoing, open-label, multicenter safety and pharmacokinetics study. The primary objectives of the Phase 1 portion are to assess the safety profile, characterize pharmacokinetics, and determine the dose schedule, the MTD, and the RPTD of venetoclax in combination with low-dose cytarabine (LCD) in treatment-naïve AML subjects. The primary objectives of the Phase 2 portion of the study are to evaluate

preliminary estimates of efficacy (including ORR and TTP) and to characterize the toxicities of the combination at RPTD. Secondary objectives of the Phase 2 portion include evaluating leukemia response (rates of CR, CRi, PR, RD, and HR including transfusion support needs) and DOR. An additional exploratory objective includes the evaluation of biomarkers that may serve as surrogate or predictors for clinical outcomes for future studies.
Of the 25 subjects in Study M14-387, 24 (96.0%) experienced at least 1 treatment-emergent adverse event. The most common adverse events for all subjects in Study M14-387 were: nausea (54%), febrile neutropenia (41%), diarrhea (44%), decreased appetite (33%), and peripheral edema (31%). Adverse events leading to study drug discontinuation occurred in 4 (16.0%) subjects, including 1 event each of disease progression, acute hepatic failure, Candida pneumonia, and subdural hemorrhage. Fatal adverse events occurred in 5 (20.0%) subjects: 2 events of malignant neoplasm progression and 1 event each of acute hepatic failure, Candida pneumonia, and lung infection.[100]

For further details of venetoclax preclinical studies, clinical studies, toxicities, pharmacokinetics, and adverse events please see the venetoclax Prescribing Label (attached).

2.4 RATIONALE FOR THE PROTOCOL

Evaluation of multiple costimulatory receptors from BM aspirates and peripheral blood in 75 AML patients (frontline and relapsed AML) as well as at baseline and every 4-8 weeks on our ongoing PD1/PD-L1 based clinical trials by 17-color flow-cytometry in the Leukemia Department in collaboration with the Immunotherapy Platform (Dr James Allison and Pam Sharma) at MDACC revealed that a number of checkpoint pathways beyond PD1/PDL1 play a role in AML, with our data supporting increased expression of OX40 and limited but identifiable expression of 4-1BB on $CD4^+$Teffector phenotype, $CD8^+$ phenotype, and $CD4^+$ Treg phenotype T-cells in bone marrow aspirates of patients with AML[15] (Williams P, et al ASH 2017 Oral presentation, abstract # 185): see updated data in section 2.6.1. These PD-1, PD-L1, OX40 expression data, the association between high PD-1/PD-L1 and poor outcome in AML, and the synergistic (often multifold improved) benefit seen with combined or sequential checkpoint blockade in multiple solid tumors supports our planned clinical trials of checkpoint blockade therapies in patients with AML. If appropriately identified, a percentage of AML and MDS patients may benefit from immunotherapy approaches targeting AML and MDS-specific immune checkpoints.

Preclinical data from PF-04518600 (OX40 mAb) suggest that it has limited efficacy as monotherapy but may have synergistic efficacy when combined with standard cytotoxic/radiation therapy or immunotherapy (e.g. OX40 + PD-L1).

Furthermore, the clinical exigency of AML requires that chemotherapy and/or targeted therapy must be used as well. Azacitidine is approved in the US and Europe for patients with MDS, and is approved in Europe and commonly used in the US to treat older patients with newly diagnosed AML. Hypomethylating agents (HMAs), azacitidine and decitabine, promote anti-tumor immune signaling by up regulation of interferon-gamma pathway genes, increased expression of HLA class 1 antigens, and activation of viral defense pathways.[106] The HMAs concurrently dampen anti-tumor immunity by increasing the expression of PD-1 and PD-L1 in solid tumors[107] and in myelodysplastic syndrome (MDS)/AML.[104] Up regulation of these immune checkpoint molecules may be a

mechanism of resistance to HMAs. Recent data shows that hypomethylating agents increase the expression of natural killer (NK)-cell activating receptors and enhanced antibody dependent cellular toxicity (ADCC) when administered in combination with a CD33-targeting ADCC inducing antibody[108]. Furthermore, prior studies from MD Anderson and others have suggested that immune checkpoints such as PD-1, PD-L1, PD-L2 and CTLA-4 are upregulated by hypomethylating agent exposure.[104,105] These preclinical data support the rationale for combination of anti-PD-L1 antibodies such as avelumab with hypomethylating agents such as azacitidine.

Following discussion and recommendations from the MDACC Department of Leukemia and Immunotherapy Platform, we propose a multi-arm study to evaluate checkpoint modulating therapies in combination with each other, and with epigenetic agents, antibody drug conjugates, and BCL-2 inhibitors in R/R AML. A combination of the glasdegib will additionally be tested in combination with an anti-CD33 monoclonal (GO) in relapsed AML.

This basket trial approach will enable the evaluation of safety, and pharmacodynamics activity of immune checkpoint modulating therapies in combination with each other, epigenetic agents, antibody drug conjugates, BCL-2 inhibitors, and other novel therapies in AML allowing rapid identification and expansion of promising arms and early closure of underperforming or excessively toxic arms. It will be of independent significance to achieve a better understanding of the tumor immunology of AML, how that is changed by immune checkpoint therapies and non-immune checkpoint therapies, and how both of these are related to clinical response, and to identify other checkpoint pathways and immune agonists that dominate the immune response in AML and develop predictive biomarkers for immunotherapies in AML. These goals will be achieved using a prespecified in-depth immune monitoring plan on bone marrow aspirate/biopsy and peripheral blood samples as specified in the correlatives section portion of this protocol. The development and execution of such master trials will hopefully help accelerate the development, identification, and selection of the most active and tolerable combinations in AML.

2.5 Clinical experience with immune checkpoints in RR AML

We treated 53 patients on the azacitidine + PD1 inhibitor (nivolumab) for relapsed/refractory AML[15] (see updated data from this trial submitted to ASH 2018, in section 2.6.2). N=35 patients were evaluable for response: N=6 (18%) achieved complete remission (CR)/ complete remission with insufficient recovery of counts (CRi) (3 CR, 3 CRi), N=5 (15%) had hematologic improvement (HI), N=9 (26%) had ≥50% BM blast reduction, N=3 patients (9%) had stable disease >6 months, and 12 (34%) had progression. The CR/CRi/HI (N=11) have been durable, with only one relapse in a patient who achieved CR/CRi/HI [CR duration; not reached (NR)]. The 4- and 8-week mortality were 0% and 6%, respectively. The median overall survival for the 35 evaluable patients was 9.3 months (range, 1.8 – 14.3) (Fig 1), and this compares favorably to historical survival with Aza-based salvage protocols in similar patients treated at MDACC (Figure 3 – Part 1 and 2).

Grade 3/4 and Grade 2 immune mediated toxicities were observed in N=7 (14%) and N=6 (12%) patients, respectively. These included 8 episodes of pneumonitis, 2 nephritis, 2 transaminitis, and 1 skin rash. In almost all cases the toxicities responded rapidly to steroids, and 12 of the 13 patients were successfully rechallenged with nivolumab without recurrence of immune toxicities. One patient has come off study due to immune

toxicity (pneumonitis). Baseline and end of cycle 1 bone marrow was evaluated on 25 of the 35 evaluable patients, including 6 responders (CR/CRi/HI) and 19 non-responders. Patients who achieved a CR/CRi/HI had a baseline higher live total CD3 (P=0.10), $CD8^+$ T-cells (P=0.02), and lower live $CD4^+Foxp3^+PD1^+$ T-regulatory (T-reg) cells (P=0.01) infiltrate in the bone marrow suggesting potential biomarkers of response. On further evaluation of post cycle 1 and post cycle 2 BM the responders demonstrate a progressive increase in the live $CD3^+$ and $CD8^+$ BM infiltrate and an increase in $CD8^+$ $ICOS^+$ activated phenotype cells. On the other hand non-responders did not have an increase in the live $CD3^+$ or T-cell subsets.

Our conclusion based on this data was that full dose azacitidine and nivolumab are tolerable and produce an encouraging response rate with durable responses in relapsed AML with poor risk features. However, combination checkpoint blockade or simultaneous blockade of inhibitory checkpoints and activation of stimulatory checkpoints may be needed to further improve the response rate and durability has been observed in many solid tumor types.

To confirm the efficacy of a hypomethylator and PD-1/PD-L1 inhibition, we activated another study of azacitidine in combination with avelumab in patients with salvage 1 or 2 AML (NCT02953561). The study includes a dose escalation run in phase to identify the MTD/DLT for the combination followed by an expansion phase to define the CRc within 3 months of initiation of the combination. This study has recently started accrual at MDACC (N=6 accrued) and the dosing, safety, and efficacy data obtained from this study will provide further background and guidance for some of the combination arms included in this study.

Figure 3: Aza+PD-1 inhibition in AML

Figure 3, Part 1

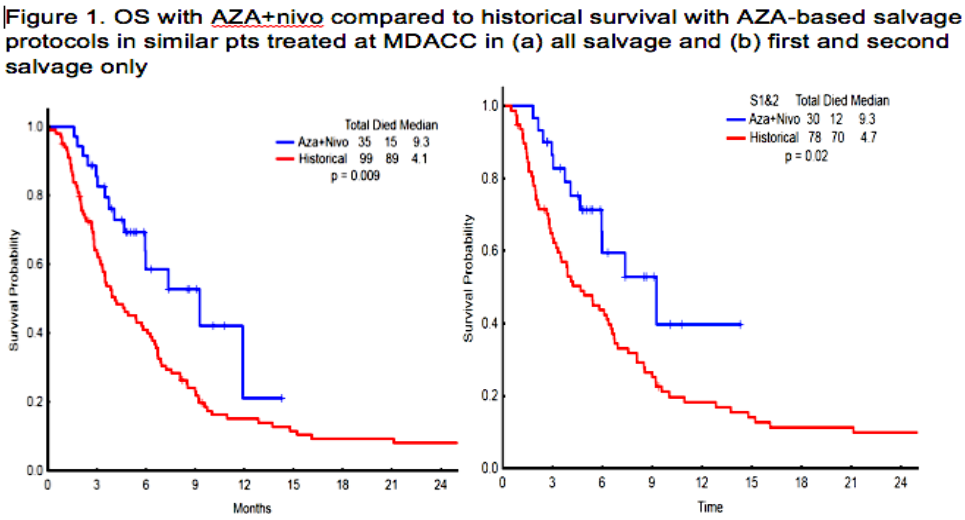
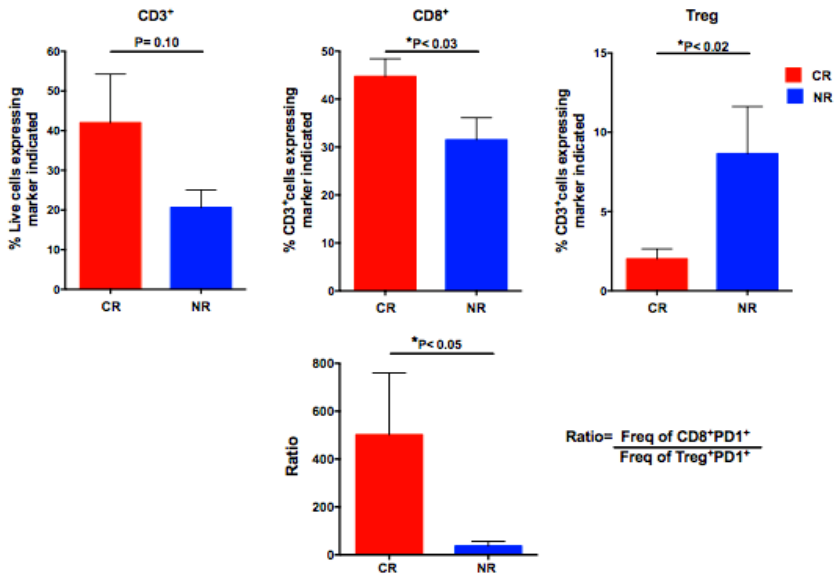


Figure 3, Part 2

Figure 2: Pretherapy T-cell subsets and T-reg activation status in bone marrow aspirate

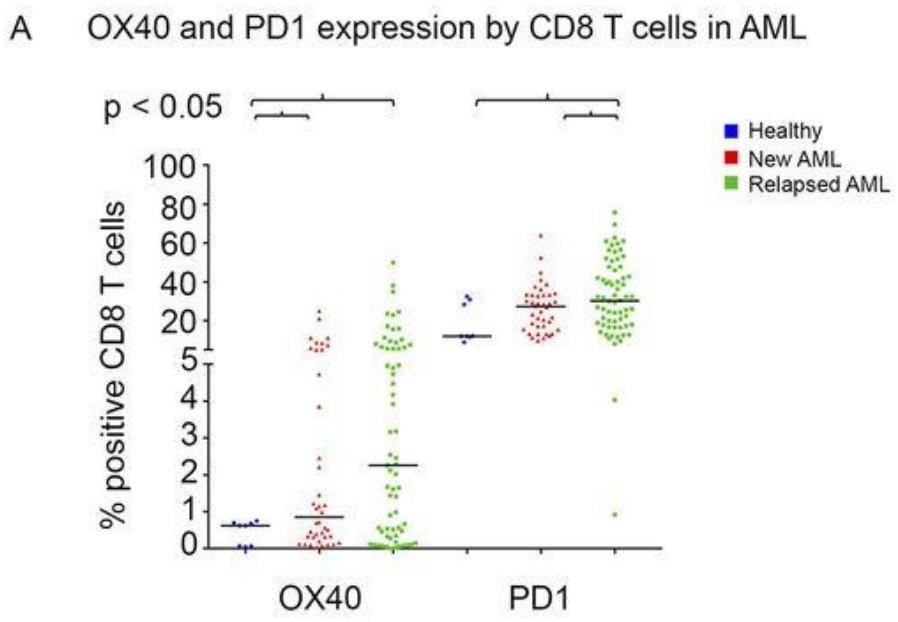


2.6 Update as of August 1, 2018

2.6.1 Immune checkpoint expression in AML

We have performed flow cytometry on bone marrow aspirates and peripheral blood mononuclear cells from 107 patients with AML (38 previously untreated, 69 relapsed/refractory) and 8 healthy donors to evaluate the distribution of T cell subsets, their expression of inhibitory (PD1, CTLA4, LAG3, TIM3) and activating (GITR, OX40, 41BB, ICOS) immune receptors, and their ligands (41BBL, B7-1, B7-2, ICOSL, Galectin 9, PD-L1, PD-L2, OX40L) on AML blasts.[109] $PD1^+$ $CD8^+$ T cells were significantly less frequent in bone marrow specimens from healthy donors (12.1%) than in the bone marrows from patients with newly diagnosed (27.3%), first relapsed (25.5%), and >1 relapsed AML (34.7%)(P<0.01; Figure 4). A similar but less pronounced trend was seen for the frequency of $OX40^+$ $CD8^+$ T cells (healthy donors versus new AML versus first relapsed AML versus >1 relapsed AML: 0.6%, 0.9%, 2.3%, and 2.1%, P=0.08). Compared with healthy donors, patients with relapsed and newly diagnosed AML had significantly higher percentage of CD8+ T cells co-expressing the inhibitory markers PD1 with TIM3 (P=0.02) and PD1 with LAG3 (P<0.01). Overall, 4-1BBL was not significantly increased in samples from either previously untreated or relapsed/refractory patients with AML, suggesting this may not be an ideal marker to target in patients with AML.

Figure 4: Increased frequency of PD1 and OX40 positive CD8 T cells in AML (N=107)



2.6.2 Updated clinical experience with hypomethylating agent in combination with immune checkpoint antibodies in AML (submitted to ASH 2018)

Patients were eligible for the azacytidine with nivolumab (AZA+Nivo) trial if they had R/R AML, ECOG ≤ 2, and adequate organ function. The recommended phase 2 dose was established as azacytidine 75mg/m^2 Days 1-7 with nivolumab 3mg/kg Day 1 and 14. Courses were repeated approximately every 4-5 weeks indefinitely. 70 R/R AML patients with median age 70 years (range, 22-90), secondary AML (44%), poor risk cytogenetics (34%), median salvage 2 (range, 1-7) were enrolled. The overall response rate was 33% including 15 CR/CRi (22%) (4 CR, 11 CRi), 1 PR, and 7 HI maintained on study >6 months (10%) without ASCT. Additionally, 6 patients (9%) remained on study with stable disease (SD) >6 months. The remaining 41 patients (58%) had no response. 8-week mortality was 10%. Patients who achieved a CR/CRi/PR/HI/SD (n=29; 42%) had significantly improved overall survival (OS) compared with NRs (n=41; 58%) (16.1 versus 4.1 months; p<0.001) (Figure 5A). By univariate analysis (UVA) improved ORR was seen in patients with pretherapy BM blast <20%, circulating WBC </=10,000/mL, *ASXL1* mutation, and no prior HMA-based therapy. By UVA improved OS was seen in patients who achieved any response or SD (CR/CRi/PR/HI/SD), were salvage 1 status, and had *ASXL1* mutation. The med OS with Aza+Nivo compared favorably to historical med OS with azacytidine-based protocols in salvage 1 or 2 patients at MDACC (6.0 versus 4.7 months; p=0.03), most prominent improvement seen in salvage 1 patients (11.1 versus 4.1 months; P<0.001) (Figure 5B). Grade 3/4 immune related adverse events were observed in 8 (11%) patients, including pneumonitis (n=3), colitis (n=2), and nephritis, skin rash, and hypophysitis (1 each). The majority (12 of 16; 75%) of these occurred in the first 8 weeks after nivolumab initiation. These responded rapidly to steroids.

As of 10/4/18, we have treated a total of 19 patients with relapsed/refractory AML in a phase Ib/II study of the combination of azacitidine and avelumab (NCT02953561). In the phase Ib portion of the study, 6 patients received avelumab at a dose of 3 mg/kg on Days 1 and 14 in combination with azacitidine 75 mg/m2 on Days 1-7, followed by 6

patients who received avelumab at a dose of 10 mg/kg on Days 1 and 14 (the maximum planned dose) in combination with azacitidine 75 mg/m2 on Days 1-7. No DLTs were observed and the MTD was not reached. The phase II portion of the study is now ongoing with the 10 mg/kg dose of avelumab in combination with standard 7-day dosing of azacitidine. Eight-four serious adverse events have occurred, including 5 serious advents at least possibly related to the azacitidine and/or avelumab (grade 2 pneumonitis, n=1; grade 3 pneumonitis, n=1; grade 3 syncope, n=1; grade 3 lung infection, n=1; grade 3 renal insufficiency, n=1). Five patients have died during the study due to sepsis (n=2), lung infection (n=1), sepsis (n=1) and unknown cause (n=1), none of which were considered related to the study treatment. One patient dropped out of the study due to sepsis, which was considered unlikely related to the study treatment. Grade 3-4 adverse events (any cause) are shown in the table below:

Adverse event	**Grade 3**	**Grade 4**
Alanine aminotransferase increased	3	
Anemia	12	
Anorectal infection	3	
Anorexia	3	
Blood bilirubin increased	3	
Colitis	3	
Diarrhea	3	
Dysphagia	3	
Dyspnea	6	
Fatigue	6	
Febrile neutropenia	24	
Gastrointestinal disorders - (Other)	3	
Generalized muscle weakness	6	
Hematuria	3	
Hypercalcemia	3	
Hyperglycemia	3	
Hypokalemia	3	
Hyponatremia	6	
Hypotension	3	
Hypoxia	3	
Infections and infestations - (Other)	24	
Left ventricular systolic dysfunction	3	
Lung infection	24	
Lymphocyte count decreased	6	4
Metabolism and nutrition disorders	3	
Nail infection	3	
Nausea	3	
Neutrophil count decreased	3	8
Pain	3	
Platelet count decreased	-	8

Pleural effusion	6	
Pneumonitis	3	
Respiratory failure	-	12
Sepsis	-	8
Skin infection	3	
Soft tissue infection	3	
Syncope	9	
Tracheostomy site bleeding	3	
Urinary tract infection	6	
Weight loss	3	

Translational biomarkers for AZA+PD1 in R/R AML

Flow-cytometry (MFC) was performed on pre- and post-therapy BMAs, after 2 doses (end of cycle 1 or EOC1) and 4 doses (EOC2) of nivolumab in 19 of 23 responders (R) (CR/CRi/PR/HI) (83%) and 28 of 41 NRs (68%). 36 parameter CyTOF was performed at same time-points in 5 responders and 5 non-responders. On pretherapy BMAs, responders had a higher frequency of $CD3^+$ (p=0.04) and $CD8^+$ cells (p=0.09) on MFC. $CD3^+$ in the pretherapy BMA with a cut-off of 13.2%, had a sensitivity of 74% and a specificity of 65% for predicting response. CD3+ was >13.2% in 26 of 47 patients (55%) who had an evaluable pretherapy BMA. Immunohistochemistry confirmed that CD3+ cells were increased in pretherapy BMs in responders. PhenoGraph clustering of all CD3-gated cells revealed 24 meta-clusters. The frequency of an effector $CD8^+$ T cell cluster (C2) expressing $CD45RA^+PD1^{lo}Tbet^{hi}Eomes^{lo}$ was significantly higher in the pretherapy BMAs of responders versus non-responders (11.2% versus 2.5%; p=0.002), and was further expanded in responders but not in non-responders in the EOC1, EOC2, and EOC4 BMAs.

Figure 5A: Overall survival in patients with response/stable disease versus non-responders (N = 70)

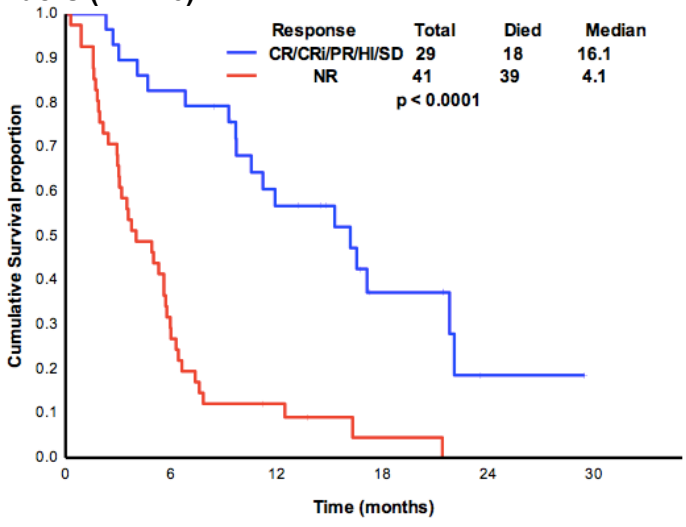
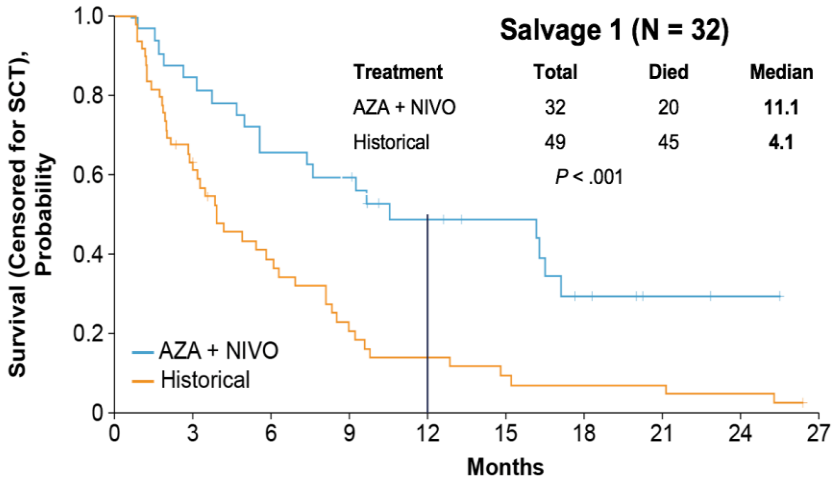


Figure 5B. Overall survival among patients who were salvage 1 versus >salvage 1 at enrollment



2.6.3 Hypomethylating agents (HMAs) in combination with GO in AML:

The combination of HMAs with GO has been evaluated in two prospective phase II clinical trials. At MD Anderson, we treated 110 patients with myeloid malignancies with decitabine and GO.[110] The patient populations, including relapsed/refractory AML with complete remission duration (CRD) <1 year (N=28, 25%); group 2: relapsed/refractory AML with CRD ≥1 year (N=5, 5%); group 3: untreated AML unfit for intensive chemotherapy or untreated myelodysplastic syndrome (MDS) or untreated myelofibrosis (MF; N=57, 52%); and group 4: AML evolving from MDS or relapsed/refractory MDS or MF (N=20, 18%). Treatment consisted of decitabine 20 mg/m2 daily for 5 days and GO 3 mg/m2 on day 5. Post-induction therapy included five cycles of decitabine+GO followed by decitabine alone. CR or CRi was achieved in 39 (35%) patients; group 1= 5/28 (17%), group 2=3/5 (60%), group 3=24/57 (42%) and group 4=7/20 (35%). The 8-week mortality in groups 3 and 4 was 16% and 10%, respectively. In another phase II study, 142 older patients with newly diagnosed AML were treated with azacitidine and GO.[111] Treatment consisted of azacitidine, 75 mg/m2 for 7 days, and gemtuzumab ozogamicin, 3 mg/m2 on day 8. The patients were stratified into good-risk (age 60-69 years or performance status 0-1) and poor-risk (age ≥70 years and performance status 2 or 3) groups. Of the 83 patients in the good-risk group, 35 (44%) achieved a CR. The median RFS and OS were 8 and 11 months, respectively. The 30-day mortality rate was 8%. In the poor-risk group, 19 (35%) achieved CR. The median RFS and OS were 7 and 11 months, respectively. The 30-day mortality rate was 14%. There were no cases of VOD in either group.

2.6.4 Venetoclax in AML

Bcl-2 inhibition: Bcl-2 overexpression has been implicated in maintaining the survival of AML cells and has been associated with resistance to chemotherapy and inferior overall survival [95] Venetoclax (formerly ABT-199/GDC-0199 is a potent and selective small-molecule inhibitor of Bcl-2 that has demonstrated cell-killing activity against a variety of leukemia cell lines, primary patient samples and leukemia stem/progenitor cells [96,97]. Venetoclax also has been found to synergize with agents known to down-regulate Mcl-1, including azacitidine.[98]

Venetoclax monotherapy in R/R AML: A phase II study has been completed evaluating single agent venetoclax in subjects with R/R AML and those unfit for intensive therapy. A total of 32 subjects were dosed. Exposure, safety, and efficacy data are available for this study.[99] The most common adverse events observed in ≥ 30% of the subjects were nausea (59.4%); diarrhea (56.3%); hypokalemia, vomiting (40.6% each); fatigue, headache (34.4% each); hypomagnesemia (37.5%); febrile neutropenia (31.3%); abdominal pain, cough, hypophosphatemia (28.1% each); epistaxis, hyperphosphatemia, hypocalcemia, malignant neoplasm progression (25.0% each); dyspnea, hypotension, peripheral edema, pyrexia, and pneumonia (21.9% each). Serious adverse events were reported in 27 subjects (84.4%), the most common being febrile neutropenia (28.1%), malignant neoplasm progression (25.0%), and pneumonia (15.6%). Three serious adverse events were considered to have a reasonable possibility of being related to venetoclax (i.e., 1 event each of diarrhea, febrile neutropenia, and pseudomonal bacteremia). No cases of TLS occurred during venetoclax treatment. In this phase II multicenter trial single agent venetoclax produced an overall response in 5/32 R/R AML patients (CR in 1 patient, CRi in 4 patients). Of the 5 patients with CR/CRi, 3 had *IDH* mutations suggesting that patients with *IDH* mutations may be particularly sensitive to venetoclax.

Venetoclax plus HMA in older patients with newly diagnosed AML: An ongoing phase Ib study has reporting promising safety and efficacy of venetoclax in combination with either azacitidine or decitabine in patients ≥65 years of age with previously untreated AML and who are ineligible for chemotherapy.[113,114] At the most recent update, 145 patients were treated with a median age of 74 years (range, 65-86 years). Cytogenetics were poor risk in 49% of patients. The 30-day and 60-day mortality rates were 3% and 8%, respectively. Tumor lysis syndrome was not observed. The CR/CRi rate for the entire cohort was 66% with a median duration of CR/CRi of 11.0 months. The median overall survival for the entire cohort was 17.5 months. These results represent the best survival data for older, unfit patients with newly diagnosed AML yet reported. Emerging clinical and exposure response data have suggested that the 400mg dose of venetoclax has the best risk-benefit profile, and a phase III study of venetoclax 400mg with azacitidine in the frontline setting is ongoing.

Venetoclax plus HMA in R/R AML: Several retrospective studies have been published evaluating the safety and efficacy of venetoclax plus an HMA in patients with R/R AML. A study from MD Anderson evaluated the outcomes of 43 patients with R/R myeloid malignancies (n=39, 91% with AML) who received venetoclax in combination with other agents.[115] Thirty-one of the evaluated patients (72%) received venetoclax with an HMA. Most patients (84%) were treated in salvage 2 or later (range 2-8) with a median of 3 prior treatment regimens. Objective response rate (ORR) was achieved in 9 (21%) patients, including 2 (5%) with CR, 3 (7%) with CRi, and 4 (9%) with morphologic leukemia-free state (MLFS). Of the 9 responding patients, all responded within 1 cycle of venetoclax combination therapy. These nine responding patients included eight (26%) of the patients treated with an HMA combination. With a median follow-up of 3 months, the estimated 6-month OS rate was 24%. In another study of venetoclax in combination with HMAs in R/R AML from City of Hope, 33 patients were treated.[116] The median number of prior therapies was 2 (range, 1-8). Twenty patients (61%) had failed HMA therapy previously and 13 patients (39%) had prior allogenic stem cell transplantation. The ORR was 64% (N=21), with 10 patients (30%) achieving CR, 7 (21%) achieving CRi and 4 (12%) achieving MLFS. With a median follow-up of 6.5 months, the 1-year OS rate was

53%. The group at Memorial Sloan Kettering Cancer Center has also reported their experience with venetoclax in combination with either low-dose cytarabine or an HMA in patients with R/R myeloid malignancies.[117] A total of 24 patients were treated (n=8 with HMA; N=16 with low-dose cytarabine). Twenty-three patients (96%) had a diagnosis of AML. The median number of prior treatments was 3 (range, 1-8); 6 patients (29%) had prior stem cell transplantation. Of 21 patients evaluable for efficacy, the ORR was 29%, including a CR rate of 24% (n=5) and PR rate of 5% (n=1). With a median follow-up of 4.1 months, the 3-month OS rate was 72%.

Pre-clinical rationale for combination of venetoclax with immune checkpoint inhibitors

In a series of human *in vitro* and *in vivo* syngeneic tumor model studies, venetoclax does not appear to antagonize anti-PD-1 therapy with nivolumab (Matthew R et al. ASH 2018, abstract #3704). Venetoclax was shown to decrease naïve but not memory T cells in *in vitro* studies of human lymphocytes. In a mixed lymphocyte reaction assay, venetoclax did not affect IFN-gamma secretion by itself or when co-treated with the checkpoint inhibitor nivolumab. Similar findings were observed in a cytomegalovirus recall assay, suggesting that venetoclax does not impair immune response to infections. In an *in vivo* experiment with the murine syngeneic tumor model MC38, venetoclax did not impair the efficacy of anti-PD-1 therapy with nivolumab, and in some studies, increased efficacy compared to either venetoclax or nivolumab monotherapy. These findings suggest that venetoclax does not impair anti-PD-1 anti-tumor therapy and may synergize with immune checkpoint therapy.

2.6.5 Rationale for protocol amendment and proposed changes

Given the emerging preclinical and clinical data outlined above, we propose an amendment to remove the 4-1BB mAb inhibitor arms and doublet arms containing IO only agents. We would instead like to add combinations that build on the doublets that have shown encouraging response rates and OS in R/R AML in recent years and have emerged as our priority regimens for patients with R/R AML, namely HMA+venetoclax and HMA+PD1/PDL1 antibody.
Specifically, we proposed the following changes:

- Removal of arms evaluating checkpoint modulating doublets: 1) OX40 mAb + avelumab, 2) OX40 mAb + azacitidine, 3) OX40 mAb + 4-1BB mAb, and 4) avelumab + 4-1BB mAb
- These arms will be replaced with arms built on a backbone of either HMA+venetoclax or HMA+avelumab: 1) azacitidine + venetoclax + GO, 2) azacitidine + avelumab + GO, and 3) azacitidine + venetoclax + avelumab

Previous arms that will be continued include: 1) OX40 mAb single-agent, which will confirm the safe dose of OX40 in AML for use in combination arms, 2) the triplet regimen of azacitidine + avelumab + OX40 mAb, and 3) GO + glasdegib.

The primary goal of this amendment is to shift to triplet regimens incorporating agents with established efficacy in AML (e.g. combination of azacitidine, GO and/or venetoclax) and to improve on commonly used doublets in RR AML such as HMA+venetoclax and HMA+PD1/PDL1 antibody.

2.7 Update as of 6/4/2019: amendment to open azacitidine + avelumab + OX40 mAb arm

To date, 4 patients have been treated with the OX40 mAb (PF-04518600) in this clinical trial. All patients were treated at the 0.3 mg/kg dose level. The number of cycles received prior to progression were 1 (n=2), 2 (n=1) and 3 (n=1). No DLTs, immune-related AEs or grade 3+ related AEs were observed. The following grade 3-5 AEs were observed all of which were attributed as unrelated to the OX40mAb: grade 3 confusion (n=1), grade 3 stroke (n=1), grade 4 sepsis (n=1), grade 4 hypotension (n=1), grade 4 ileus (n=4), grade 3 febrile neutropenic fever (n=3) and grade 5 multi-organ failure.

In a parallel phase I/II study in patients with advanced solid tumors (NCT03217747), 51 patients have been treated with OX40 mAb combinations as of 5/9/19. All patients received the OX40 mAb at a dose of 0.3 mg/kg. Twenty-two patients received avelumab + OX40 mAb, 22 received avelumab + OX40 mAb + 4-1BB mAb, 3 received avelumab + OX40 mAb + irradiation, and 4 received avelumab + OX40 mAb + 4-1BB mAb + irradiation. No DLTs have been observed in any of these cohorts. A total of 9 AEs (in 6 total patients) were attributed as at least possibly related to the OX40 mAb, and all were grades 1 or 2. These AEs included: grade 1 fatigue (n=1), grade 1 alkaline phosphatase elevation (n=1), grade 1 rash (n=2), grade 2 rash (n=1), grade 2 pruritus (n=1), grade 2 mucositis (n=1), grade 1 anorexia (n=1), grade 2 lipase elevation (n=1). Two patients died within 30 days of the first treatment dose (1 patient on avelumab + OX40 mAb + 4-1BB mAb arm, and 1 patient on the OX40 mAb + 4-1BB mAb arm). Both patients were taken off study prior to death (1 for progressive disease and 1 for withdrawal of consent). Both deaths were attributed to underlying disease and assessed as unrelated to the study treatment.

In sum, the OX40 mAb appears safe in these ongoing clinical trials, with no DLTs or related grade 3-5 AEs observed to date, with 55 patients treatment with OX40 mAb as a single-agent or in combinations to date. Given the rapidly changing treatment landscape of AML and the established safety of OX40 mAb (PF-04518600) alone and in combinations, we propose an amendment to close cohort A (i.e. OX40 mAb as single agent) and open cohort E (i.e. combination of azacitidine + avelumab + OX40 mAb).

2.8 Update as of 3/18/20: amendment to close OX40 mAb monotherapy, GO + glasdegib, and azacitidine + avelumab + OX40 mAb arms

Since the last update (see section 2.7 above), no additional patients have been treated on the OX40 mAb (PF-04518600) single-agent arm (Arm A). Although this agent was safe in this trial and in other studies in solid tumors, given the limited clinical activity in solid tumors and the changing landscape of AML therapy with encouraging therapies becoming available and focus transitioning to safe doublets and triplet based therapies, we propose to close this arm. Given the lack of single-agent activity of the OX40 mAb, we also propose to close the azacitidine + avelumab + OX40 mAb arm (Arm E) as the other triplets are of higher clinical interest.

To date, 5 patients have been treated with GO + glasdegib (Arm F). Three patients were evaluable for response and none responded after one cycle. The other 2 patients were not evaluable for response due to death prior to response assessment (considered

unrelated to the study drug). Overall, no DLTs were observed in the 3 evaluable patients. However, due to the apparent lack of clinical activity and similarly availability of other doublets and triplets with encouraging activity and stronger clinical/preclinical rationale at our center, we propose to close this arm and focus on patient accrual in the arms containing of triplet regimens with venetoclax and/or GO (i.e. Arms B-D).

3.0 STUDY DESIGN

- This will be a phase IB, multiple, parallel, and sequential arm, open-label, non-randomized study with no crossover permitted between the arms.

3.1 Study Design Overview (Table 1)

Table 1: Study Schema and Schedule Overview

Indication	Treatment Arm	Treatment	Dosing	Escalation/ de-escalation	Major Endpoints	Fixed N (Apply stopping rules)
Salvage AML	**A**	OX40 (PF-04518600) alone	D1 and D14 of a 4 wk cycle	4 patients	RP2D/MTD	Closed (as of 6/4/19) 4 treated
	B	Azacitidine + venetoclax + GO	-Aza D1-7 of a 4wk cycle -Ven D1-28 -GO D8		1. CR/CRp/PR per IWG2003	30
	C	Azacitidine + GO + avelumab	-Aza D1-7 of a 4wk cycle -GO D8 -Avelumab D1 and D14		1. CR/CRp/PR per IWG2003	24
	D	Azacitidine + venetoclax + avelumab	-Aza D1-7 of a 4wk cycle -Ven D1-28 Avelumab D1 and D14		1. CR/CRp/PR per IWG2003	24
	E	Azacitidine + avelumab + OX40	-Aza D1-7 of a 4wk cycle -Both OX40 and avelumab D1 and D14		1. CR/CRp/PR per IWG2003	Closed (as of 3/18/20) 0 treated
	F	GO + Glasdegib	Glasdegib po daily in 4 wk cycle -GO D1, D4 and D7		1. CR/CRp/PR per IWG2003	Closed (as of 3/18/20) 5 treated

3.2 Safety evaluation for Arm A (OX40 mAb alone in RR AML):

DLT is defined in section 3.4. A maximum of 4 patients will be enrolled in one dose level.

Only the 0.3 mg/kg dose of OX40 will be evaluated as this was the dose selected to move forward from the solid tumor OX40 single agent dose finding study (B0601002, ClinicalTrials.gov NCT02315066). Up to four patients will be enrolled at the dose level of 0.3mg/kg of OX40. If no more than 1 out of the 4 patients experienced a DLT, then this dose of OX40 will be established as the RP2D for AML and used in the subsequent combinations incorporating OX40 mAb.

3.3 DLT monitoring in each arm (B-F):

Each arm in the study will accrue up to 21 patients (Arms E-F) or up to 24 patients (Arms C-D) and 30 patients (Arm B) with pre-defined toxicity stopping rules to be implemented for early DLT evaluation as per following plan:
Evaluation of the first 6 patients in each treatment arm will occur after all patients have completed two cycles of treatment (or at least 56 days from the first day of treatment). Enrollment will be halted while the first 6 patients in each treatment arm are evaluated for safety. The treatment combination will be considered as safe, and continue to enroll to a total of 21 patients (Arms E-F) or 24 patients (Arms C-D) or 30 patients (Arm B) when there are no more than 1 out of 6 patients with DLTs in the first cycle of treatment. If any patients in the first 6 of each treatment arm withdraw from the study without a DLT event prior to completing the first cycle of treatment, they will be replaced for the assessment of DLT rate. This will allow for early identification of significant toxicities and early stoppage in potentially toxic arms. If 2 or more out of 6 patients have DLTs in the first cycle of treatment in any arm, then an additional 6 patients will enroll at a next lower dose level to be determined by the PI, sponsor (MDACC IND office), and Pfizer team after reviewing the safety, efficacy, and PD data from the first 6 patients enrolled. If no more than 1 out of the additional 6 patients treated with the lower dose level experience DLTs, this treatment combination will be considered as safe and continue to enroll to a total of 21 patients (Arms E-F) or 24 patients (Arms C-D) or 30 patients (Arm B). If 2 or more out of these 6 additional patients experienced DLTs, then this arm will be halted.

The Investigator is responsible for completing the cohort summary template and submitting to the IND office Medical Monitor for review and approval prior to continuing accrual beyond each set of 6 patients in each arm of the study. A copy of the cohort summary should be placed in the Investigator's Regulatory Binder under "sponsor correspondence". This should be submitted after the first six patients.

3.4 DLT Definition

DLT is defined as clinically significant non-hematologic adverse event or abnormal laboratory value assessed as unrelated to disease progression, intercurrent illness, or concomitant medications and occurring during the first cycle (28 days) on study that meets any of the following criteria:

- CTCAE Grade 3 AST (SGOT) or ALT (SGPT) for >/= 7 days or grade 3 hyperbiliribunemia for >/= 7 days

- CTCAE Grade 3 AST (SGOT) or ALT (SGPT) accompanied by grade 2 bilirubin increase

- CTCAE Grade 4 AST (SGOT) or ALT (SGPT) of any duration

- All other clinically significant non-hematological adverse event that is Grade 3 or 4 according to the NCI common terminology criteria version 4.0 with the following exceptions:

  - Grade 3 or 4 nausea, vomiting and diarrhea will be considered DLT only if not controlled by optimal therapy within 72 hours.

  - Grade 3 biochemical abnormalities (e.g., lipase or bilirubin elevation) will only be considered DLT if accompanied by clinical consequences. Grade 3 or 4 electrolyte abnormalities will only be considered DLT if possibly related to study drug and not corrected by optimal replacement therapy within 72 hours.

- Results in discontinuation of therapy

- Any treatment-related death;

Grade 4 neutopenia lasting ≥ 42 days from start of cycle in absence of evidence of active AML.

For patients in venetoclax-containing arms (i.e. Arms B and D) who do not receive venetoclax on day 1 due to logistical and/or financial reasons, the DLT period will be extended to 28 days from the first dose of venetoclax. For evaluation of neutropenia-related DLT, the DLT period will be 42 days from the first dose of venetoclax. Evaluation of the first 6 patients in each of the venetoclax containing treatment arms (arms B and D) will occur after all patients have completed two cycles of treatment (or at least 56 days from the first dose of venetoclax). Enrollment will be halted while the first 6 patients in each of these treatment arms are evaluated for safety.

Please see statistics section (section 11.0) for efficacy and toxicity stopping rules to be applied independently to each cohort.

3.5 Cohort enrollment schema

(A) Arms B-E (Azactidine + venetoclax + GO; azacitidine + avelumab + GO; azacitidine + venetoclax + avelumab; azacitidine + avelumab + PF-04518600)

Arms B-E will commence enrollment in parallel with the OX40 arm (namely Arm A). If multiple are open to enrollment the patient allocation will generally follow a rotating sequence between arms unless the PI (or Co-PI) decide to allot a patient to a particular arm. There will be no separate escalation/dose finding cohorts for

these combination arms, but predefined toxicity stopping rules have been built in to monitor for grade 3/4 drug-related toxicities and to stop or de-escalate dose if >30% grade 3/4 drug-related toxicity is observed in any of the combination arms at any given time as outlined in section 3.3 (DLT monitoring in each arm).

(B) Arm F (GO + Glasdegib)

Arm F is the combination of GO + glasdegib. This arm will commence enrollment in parallel with the OX40 arm (namely Arm A). There will be no separate escalation/dose finding cohorts these combination arms but we have built in predefined toxicity stopping rules to monitor for grade 3/4 drug-related toxicities and to stop or de-escalate dose if >30% grade 3/4 drug-related toxicity is observed in any of the combination arms at any given time as outlined in section 3.0 (DLT monitoring in each arm).

4.0 PATIENT SELECTION

4.1 Inclusion Criteria

4.1.1 Patients with AML who are refractory or relapsed (any salvage) with no available therapies or not candidates for available therapies. For patients with prior MDS or chronic myelomonocytic leukemia (CMML) or MPN who transformed to AML, therapy received for MDS, CMML, or MPN is NOT considered as prior therapy for AML with the exception of MDS or CMML treated with HMAs. Patients with MDS or CMML treated with HMA therapies who progress to AML, and have no available therapies or are not candidates for available therapies, will be eligible at the time of progression to AML.

4.1.2 Prior therapy with hydroxyurea, chemotherapy, biological or targeted therapy (e.g. FLT3 inhibitors, other kinase inhibitors), or hematopoietic growth factors is permitted.

4.1.3 Age >/=18 years

4.1.4 Eastern Cooperative Oncology Group (ECOG) Performance Status ≤2

4.1.5 Adequate organ function: total bilirubin ≤2.0 times upper limit of normal (x ULN); aspartate aminotransferase or alanine aminotransferase ≤2.5 x ULN (aspartate aminotransferase or alanine aminotransferase ≤5.0 x ULN if deemed related to leukemia by the treating physician)

4.1.6 Adequate renal function defined by an estimated creatinine clearance ≥ 40 mL/min according to the Cockcroft-Gault formula (or local institutional standard method)

4.1.7 Patients must provide written informed consent.

4.1.8 In the absence of rapidly progressive disease, the interval from prior treatment to the time of initiation of protocol therapy will be at least 14 days for prior anti-leukemic therapy with the exception of hydroxyurea as noted below, OR at least 5 half-lives for cytotoxic/noncytotoxic agents, whichever is shorter. The half-life for the therapy in question will be based on published pharmacokinetic literature (abstracts, manuscripts, investigator brochure's, or drug-administration manuals) and will be documented in the protocol eligibility document. The toxicity from prior therapy should have resolved to Grade ≤1, however alopecia and sensory neuropathy Grade ≤2 not constituting a safety risk based on investigators judgement is acceptable. Since the effect of most IO-agents, HMA-therapies, SMO-inhibitors, venetoclax may be delayed, use of hydroxyurea for patients with rapidly proliferative disease is allowed before the start of study therapy and will not require a washout.

4.1.9 Concurrent therapy for CNS prophylaxis or continuation of therapy for controlled CNS disease is permitted. Patients with a known history of CNS disease or leukemic brain metastasis must have been treated locally, have at least 3 consecutive LPs with no evidence of CNS leukemia, and must be clinically stable for at least 4 weeks prior to enrollment and have no ongoing neurological symptoms that in the opinion of the treating physician are related to the CNS disease (sequelae that are a consequence of the treatment of the CNS disease are acceptable).

4.1.10 Females must be surgically or biologically sterile or postmenopausal (amenorrheic for at least 12 months) or if of childbearing potential, must have a negative serum or urine pregnancy test within 72 hours before the start of the treatment.

4.1.11 Women of childbearing potential must agree to use an adequate method of contraception during the study and until 3 months after the last treatment. Males must be surgically or biologically sterile or agree to use an adequate method of contraception during the study until 3 months after the last treatment.

Adequate methods of contraception include:

- Total abstinence when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.
- Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy) or tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment
- Male sterilization (at least 6 months prior to screening). For female patients on the study, the vasectomized male partner should be the sole partner for that patient
- Combination of any of the two following (a+b or a+c or b+c)

a. Use of oral, injected or implanted hormonal methods of contraception or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception
b. Placement of an intrauterine device (IUD) or intrauterine system (IUS)
c. Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/ vaginal suppository

In case of use of oral contraception, women should have been stable on the same pill before taking study treatment.

Note: Oral contraceptives are allowed but should be used in conjunction with a barrier method of contraception due to unknown effect of drug-drug interaction.

Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential.

4.2 Exclusion Criteria

4.2.1 Patients with a known allergy or hypersensitivity to the protocol therapies or any of their components to be used in the arm the patient is to be enrolled on. Known severe hypersensitivity reactions to monoclonal antibodies (Grade ≥ 3 NCI-CTCAE v 4.03), any history of anaphylaxis, or uncontrolled asthma (that is, 3 or more features of partially controlled asthma).

4.2.2 Patients with a known history of severe interstitial lung disease or severe pneumonitis or active pneumonitis/pneumonia or pulmonary pathology that is not well controlled in the opinion of the treating physician and/or PI.

4.2.3 Clinically significant (i.e., active) cardiovascular disease: acute cerebral vascular accident/stroke (< 6 months prior to enrollment) excluding TIA, myocardial infarction (< 6 months prior to enrollment), unstable angina, congestive heart failure (≥ New York Heart Association Classification Class II), or serious cardiac arrhythmia requiring medication.

4.2.4 Ejection fraction < 50% on screening ECHO or MUGA for patients in glasdegib-containing arm

4.2.5 Persisting toxicity related to prior therapy of Grade >1 NCI-CTCAE v 4.03; however, alopecia and sensory neuropathy Grade ≤ 2 is acceptable

4.2.6 Active autoimmune disease that might deteriorate when receiving an immunostimulatory agent:

a. Subjects with diabetes type I, vitiligo, psoriasis, hypo- or hyperthyroid disease not requiring immunosuppressive treatment are eligible
b. Current use of immunosuppressive medication, EXCEPT for the following: a. intranasal, inhaled, topical steroids, or local steroid injection (e.g., intra-articular injection); b. Systemic corticosteroids at physiologic doses ≤ 10 mg/day of prednisone or equivalent; c. Steroids as premedication for hypersensitivity reactions (e.g., CT scan premedication).

4.2.7 Prior organ transplantation including allogenic stem-cell transplantation within 3 months prior to planned enrollment.

4.2.8 Patients with symptomatic CNS leukemia or patients with poorly controlled CNS leukemia.

4.2.9 Active and uncontrolled disease (active infection requiring systemic therapy, fever likely secondary to infection within prior 48 hours, uncontrolled hypertension despite adequate medical therapy as judged by the treating physician.

4.2.10 Known history of testing positive for HIV or known acquired immunodeficiency syndrome

4.2.11 Known history of Hepatitis B virus (HBV) or hepatitis C virus (HCV) infection at screening (positive HBV surface antigen or HCV RNA if anti-HCV antibody screening test positive

4.2.12 Vaccination within 4 weeks of the first dose of avelumab and while on trials is prohibited except for administration of inactivated vaccines

4.2.13 Other severe acute or chronic medical conditions that is active and not well controlled including colitis, inflammatory bowel disease, or psychiatric conditions including recent (within the past year) or active suicidal ideation or behavior; or laboratory abnormalities that may increase the risk associated with study participation or study treatment administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the patient inappropriate for entry into this study.

4.2.14 Patients unwilling or unable to comply with the protocol.

4.2.15 Pregnant or breastfeeding

4.2.16 Known alcohol or drug abuse within the last 1 year

4.2.17 Acute promyelocytic leukemia (APL).

4.2.18 Cardiac exclusions specific to Glasdegib and OX40 containing arms: Any one of the following ongoing or in the previous 6 months: congenital long QT syndrome, Torsades de pointes, sustained ventricular tachyarrhythmia, right or left bundle branch block and bifascicular block, unstable angina, coronary/peripheral artery bypass graft, CVA, transient ischemic attack or symptomatic pulmonary emboli, as well as bradycardia defined as <50 bpms. Active cardiac dysrhythmias of NCI CTCAE grade >/= 2 (eg, atrial fibrillation) or QTcF interval > 470 msec

5.0 TREATMENT PLAN

5.1 General
All patients will be registered through CORe.

5.2 Schedule
The Investigator is responsible for completing Safety/Efficacy Monitoring summary reports and submitting to the IND office Medical Affairs and Safety Group for review and approval. These should be submitted as follows:

- Arm A:
  Every 4 evaluable subjects, after completion of 28 days of study treatment. Study enrollment of this arm must be held until IND approval is obtained.

- Lead-In and Phase II for Arms B to F:
  - Safety monitoring
    - Lead-in: After the first 6 evaluable subjects, per arm, complete 2 cycles of therapy and every 3 evaluable subjects, per arm, thereafter. Enrollment must be halted for that individual arm while the first 6 patients of that arm are evaluated for safety (i.e. after all patients have received 2 cycles of therapy, or been followed for at least 56 days from the start of treatment or at least 56 days from the first dose of venetoclax in the venetoclax containing arms B and D).
    - Phase II: After the first 6 evaluable subjects, per arm, complete 2 cycles of therapy and every 3 evaluable subjects, per arm, thereafter.
  - Futility monitoring
    - Futility summary will be submitted after the first 10 evaluable subjects, per arm, complete 3 cycles of therapy and every 5 evaluable subjects, per arm, thereafter.

The dosing calculations should be based on the body weight. All doses should be rounded to the nearest milligram for all agents. There will be no dose reductions (only interruptions when indicated) allowed for avelumab and PF-04518600 on this trial.

Patients will be treated according to the following schedules that are specific to each arm:

(A) Arm A (PF-04518600 alone in RR AML) (6 patient dose-finding cohort):
PF-04518600 will be administered as an intravenous infusion over 60 minutes (+/- 30 minutes) on Day 1 and 14 (+/- 2 days) of each 28-day (+/- 4 day) cycle. This regimen may be modified based on local treatment standards and guidelines. If the patient develops an infusion-related reaction, prophylactic premedications can be added for future infusions, at the discretion of the PI and/or treating physician. PF-04518600 should be administered in a setting that allows for immediate access to an intensive care unit or equivalent environment and administration of therapy for anaphylaxis, such as the ability to implement immediate resuscitation measures. Steroids (e.g. dexamethasone 10 mg), epinephrine (1:1,000 dilution), allergy medications (IV antihistamines), bronchodilators, or equivalents, and oxygen should be available for immediate access. Following completion of the infusions, patients must be observed for 2 hours post-infusion for potential infusion-related reactions. The ambulatory treatment center/inpatient nurse will use the institutional flowsheet to document observation of the patient as per institutional standards. If the patients tolerate the first two infusions of PF-04518600 without any reactions the observation period for potential infusion-related reactions can be reduced to 1 hour for subsequent infusions.

The dose level of 0.3 mg/kg selected for PF-04518600 monotherapy portion of this study was the dose levels found to be of interest and selected for further evaluation in the solid tumor PF-04518600 monotherapy dose-finding study (Study B0601002).

- The dose and /or schedule of administration is subject to modification pending information from other ongoing clinical trials of PF-04518600 as a single agent and in combination with other drugs.

- DLT definition are provided in section 3.4. Patients that are removed from study before day 28 for any reason other than toxicity and have not experienced DLT will be replaced. Patients not evaluable for DLT will be replaced. Patients experiencing DLT may continue therapy on trial after discussion with the PI if they are having clinical benefit or if in the best interest of the patient and the reasons for continuation and potential benefit/risk profile for the patient must be clearly documented in the medical records.

- One cycle of therapy is defined as 28 days (+/- 4 days) or 4 weeks. Patients will receive one cycle of therapy every 28 days (+/- 4 days). During the DLT evaluation period the cycle must be a minimum 28 days.

(B) Arm B (Azacitidine + venetoclax + GO in RR AML): N= Up to 26

- Azacitidine will be administered subcutaneously (SQ) or intravenously (IV) for the first 7 days of every cycle with daily schedule of 7 consecutive days (Days 1-7) or for days 5-2-2 which is 5 consecutive weekdays (Days 1-5) with rest on the 2 weekend days (Days 6 and 7) and then dosing the first two weekdays of the next week (Days 8 and 9) of each 28-day cycle (+/- 4 days) as determined by treating physician. Both SQ and IV forms of administration are FDA approved and considered interchangeable. Patients may start receiving azacitidine by one route and changed to the other, and also administration schedules from one schedule and changed to the other at any time as needed based on patient and/or physician preference.

- Venetoclax will be given orally on days 1-28 of cycle 1 and days 1-21 of subsequent cycles. During cycle 1, venetoclax will be dose escalated daily to the goal dose of 400mg daily. Patients will receive 100mg on day 1, 200mg on day 2 and 400mg on day 3 and onwards. This dosing applies to patients in both Phase I and II components of this study.

  To minimize the risk of tumor lysis syndrome (TLS), All patients will be hospitalized for the entirety of the venetoclax dose escalation starting at least on day -1 of treatment initiation and until 24 hours after the completion of venetoclax dose escalation. To mitigate the risk for TLS, subjects must be receiving tumor lysis prophylaxis, including hydration (oral, intravenous) and treatment with a uric acid reducing agent (allopurinol, rasburicase) prior to and during the venetoclax ramp up period of Cycle 1. Physicians should leukoreduce with hydroxyurea to reduce the peripheral white blood count to below 15,000/μL prior to the administration of the first dose of venetoclax. If the WBC is >15,000/μL the venetoclax should not be initiated till the white count is brought down to below 15,000/μL
  As venetoclax is obtained commercially, some patients may have delays in beginning venetoclax due to financial or other logistical considerations. Even if venetoclax is not yet available, patients may begin azacitidine on day 1. Venetoclax should be started when it is obtained and continued as above (i.e. through day 28). Failure to begin venetoclax on day 1 will not be considered a protocol deviation.

  TLS chemistry tests (potassium, uric acid, creatinine, calcium and phosphorus) will be obtained prior to dosing and 6-8 hours after each new venetoclax dose. TLS chemistry test results will be reviewed by the investigator in real time and prior to the subject receiving the next higher dose of venetoclax to ensure appropriate and timely management. If a subject meets criteria for clinically significant laboratory or clinical TLS, no additional venetoclax should be administered until resolution of the TLS. Venetoclax interruption for up to 72 hours following transient (< 48 hours) chemical changes and laboratory TLS will be allowed and will not require a dose reduction.

  In cycle 1, patients should undergo a bone marrow aspiration/biopsy on day 21 (+/- 3 days). Patients who achieve marrow remission (i.e. bone marrow blasts <5%) or marrow aplasia/hypoplasia (</=10% cellularity or insufficient sample) should discontinue venetoclax and be monitored for count recovery.

  a) If the Day 21 bone marrow shows <5% blasts, the venetoclax should be held on Day 21, and cycle 2 should not be initiated till ANC>0.5 and platelets are >30K without platelet transfusion support for >5 days.

  b) If the Day 21 bone marrow shows aplasia/hypoplasia (</=10% cellularity or insufficient sample), the venetoclax should be held on Day 21, and a repeat bone marrow should be performed on Day 28 (+/- 3 days). If the Day 28 bone marrow shows >/=5% blasts proceed with cycle 2 if this is in the best interest of the patient. If the Day 28 bone marrow shows <5% blasts, the venetoclax should continue to be held, and cycle 2 should not be initiated till ANC>0.5 and platelets are >30K without platelet transfusion support for >5 days. If the

Day 28 bone marrow shows persistent aplasia/hypoplasia (</=10% cellularity or insufficient sample) continue to hold the venetoclax and repeat a bone marrow in 10-12 days.

c) If a bone marrow remission (<5% blasts) or aplasia/hypoplasia is not confirmed on the Day 21 bone marrow, patients should continue venetoclax until day 28 and have a repeat bone marrow on Day 28 (+/- 3 days). If the Day 28 bone marrow shows >/=5% blasts proceed with cycle 2 if this is in the best interest of the patient. If the Day 28 bone marrow shows <5% blasts or aplasia/hypoplasia follow steps outlined in “a” and “b” above.

Treatment interruptions and dosing schedules other than the ones mentioned above can be considered after discussion with the PI and proper documentation of the rationale.

- The recommended starting dose of GO in this arm is 3 mg/m^2 on Day 8. In order to mitigate potential toxicity, the dose may be capped at 4.5 mg at the discretion of the treating physician. GO will not be administered for a longer duration or repeated beyond the Day 8dosing. The GO solution, following reconstitution and dilution in saline, can be infused to deliver the dose over a 2-hour period on Day 8. During the infusion, only the syringe or IV bag needs to be protected from light. GO should never be administered as an IV push or bolus.

  In order to lessen the risk of infusion reactions associated with GO, it is recommended that patients receive the following prophylactic medications one hour before GO administration: diphenhydramine 50 mg PO and acetaminophen 650-1000 mg PO. Thereafter, two additional doses of acetaminophen 650-1000 mg PO, one every 4 hours, and additional diphenhydramine may be administered as needed. For first infusion, vital signs should be checked prior to the infusion, every 15 minutes (+/- 10 minutes) during infusion, at end of infusion (+/- 10 minutes) and 60 minutes (+/- 30 minutes) after end of infusion. For subsequent infusions, vital signs should be checked prior to the infusion, every 30 minutes (+/- 15 minutes) during infusion, at end of infusion (+/- 10 minutes) and 60 minutes (+/- 30 minutes) after end of infusion. The ambulatory treatment center/inpatient nurse will use the institutional flowsheet to document observation of the patient as per institutional standards. Additionally, methylprednisolone can be given prior to GO infusion to further decrease the risk of infusion-related symptoms. In case of infusion reactions during administration, study drug infusion should be stopped and appropriate medication should be given (e.g., diphenhydramine, acetaminophen, and methylprednisolone). Once symptoms have resolved, reinfusion at a lower rate (e.g., 50% slower) may be attempted. In the event of a serious anaphylactic reaction during administration of GO, the infusion should be stopped and the patient treated as clinically indicated. Re-infusion of GO under these circumstances is NOT recommended.

  Physicians should consider leukoreduction with hydroxyurea or leukapheresis to reduce the peripheral white blood count to below 30,000/µL prior to administration of GO and appropriate measures (e.g., hydration and allopurinol) must be taken to minimize hyperuricemia and the potential for renal impairment due to tumor lysis. Patients should be closely monitored for signs and laboratory changes suspicious for VOD including weight gain, right upper quadrant pain,

lower extremity edema, transaminitis or bilirubin increase. A right upper quadrant ultrasound with Doppler flow should be obtained if there is clinical suspicion for VOD. Further work-up for VOD may include a liver biopsy at the discretion of the treating physician. Therapy with GO should be stopped if there is any clinical concern for VOD.

The dose of GO should be held if total bilirubin > 2 x ULN or if AST or ALT > 2.5 x ULN. If laboratory studies return to acceptable range, then the dose of GO may be made up later in the cycle at the discretion of the treating physician after consultation with the PI.

- Following completion of the infusions, it is recommended to be observed for 2 hours post-infusion for potential infusion-related reactions. The ambulatory treatment center/inpatient nurse will use the institutional flowsheet to document observation of the patient as per institutional standards.

(C) Arm C (Azacitidine + avelumab + GO in RR AML): N= Up to 26

- Azacitidine will be administered subcutaneously (SQ) or intravenously (IV) for the first 7 days of every cycle with daily schedule of 7 consecutive days (Days 1-7) or for days 5-2-2 which is 5 consecutive weekdays (Days 1-5) with rest on the 2 weekend days (Days 6 and 7) and then dosing the first two weekdays of the next week (Days 8 and 9) of each 28-day cycle (+/- 4 days) as determined by treating physician. Both SQ and IV forms of administration are FDA approved and considered interchangeable. Patients may start receiving azacitidine by one route and changed to the other, and also administration schedules from one schedule and changed to the other at any time as needed based on patient and/or physician preference.

- Avelumab infusion at a dose of 10 mg/kg (maximum dose: 2000 mg) should begin 30-60 minutes after the completion of azacitidine on day 1, as described above, whenever possible. A second dose of avelumab will be administered on Day 14 of each 28 day cycle. Premedication with an antihistamine and with paracetamol (acetaminophen) (for example, 25-50 mg diphenhydramine and 500-650 mg paracetamol [acetaminophen] IV or oral equivalent) is mandatory and recommended to be given approximately 30 to 60 minutes prior to each dose of avelumab. This regimen may be modified based on local treatment standards and guidelines as appropriate provided it does not include systemic corticosteroids.

- The recommended starting dose of GO in this arm is 3 mg/m^2 on Day 8. In order to mitigate potential toxicity, the dose may be capped at 4.5 mg at the discretion of the treating physician. GO will not be administered for a longer duration or repeated beyond the Day 8 dosing. The GO solution, following reconstitution and dilution in saline, can be infused to deliver the dose over a 2-hour period on Day 8. During the infusion, only the syringe or IV bag needs to be protected from light. GO should never be administered as an IV push or bolus. Prevention and monitoring of infusion reactions and tumor lysis syndrome and monitoring for VOD and hold parameters will be as outlined in Arm B.

- Following completion of the infusions, it is recommended to observed patients for

2 hours post-infusion for potential infusion-related reactions. The ambulatory treatment center/inpatient nurse will use the institutional flowsheet to document observation of the patient as per institutional standards.

(D) Arm D (Azacitidine + venetoclax + avelumab in RR AML): N= Up to 26

- Azacitidine will be administered subcutaneously (SQ) or intravenously (IV) for the first 7 days of every cycle with daily schedule of 7 consecutive days (Days 1-7) or for days 5-2-2 which is 5 consecutive weekdays (Days 1-5) with rest on the 2 weekend days (Days 6 and 7) and then dosing the first two weekdays of the next week (Days 8 and 9) of each 28-day cycle (+/- 4 days) as determined by treating physician. Both SQ and IV forms of administration are FDA approved and considered interchangeable. Patients may start receiving azacitidine by one route and changed to the other, and also administration schedules from one schedule and changed to the other at any time as needed based on patient and/or physician preference.

- Avelumab infusion at a dose of 10 mg/kg (maximum dose: 2000 mg) should begin 30-60 minutes after the completion of azacitidine on day 1, as described above, whenever possible. A second dose of avelumab will be administered on Day 14 of each 28 day cycle. Premedication with an antihistamine and with paracetamol (acetaminophen) (for example, 25-50 mg diphenhydramine and 500-650 mg paracetamol [acetaminophen] IV or oral equivalent) is mandatory and recommended to be given approximately 30 to 60 minutes prior to each dose of avelumab. This regimen may be modified based on local treatment standards and guidelines as appropriate provided it does not include systemic corticosteroids.

- Venetoclax will be given orally on days 1-28 of cycle 1 and on days 1-21 of subsequent cycles. During cycle 1, venetoclax will be dose escalated daily to the goal dose of 400mg daily. Patients will receive 100mg on day 1, 200mg on day 2 and 400mg on day 3 and onwards. Prevention of TLS and need for day 21 bone marrow aspiration in cycle 1 to decide on continued venetoclax administration will be as outlined in Arm B. This dosing applies to patients in both Phase I and II components of this study.

As venetoclax is obtained commercially, some patients may have delays in beginning venetoclax due to financial or other logistical considerations. Even if venetoclax is not yet available, patients may begin the combination of azacitidine and avelumab on day 1. Venetoclax should be started when it is obtained and continued as above (i.e. through day 28). Failure to begin venetoclax on day 1 will not be considered a protocol deviation.

- Avelumab infusion at a dose of 10 mg/kg should begin 30-60 minutes after the completion of azacitidine on day 1, as described above, whenever possible. A second dose of avelumab will be administered on Day 14 of each 28-day cycle.

- Following completion of the infusions, it is recommended to observe patients for 2 hours post-infusion for potential infusion-related reactions. The ambulatory treatment center/inpatient nurse will use the institutional flowsheet to document observation of the patient as per institutional standards.

(E) Arm E (Azacitidine + avelumab + PF-04518600 in RR AML): N= Up to 21

- Azacitidine will be administered subcutaneously (SQ) or intravenously (IV) for the first 7 days of every cycle with daily schedule of 7 consecutive days (Days 1-7) or for days 5-2-2 which is 5 consecutive weekdays (Days 1-5) with rest on the 2 weekend days (Days 6 and 7) and then dosing the first two weekdays of the next week (Days 8 and 9) of each 28-day cycle (+/- 4 days) as determined by treating physician. Both SQ and IV forms of administration are FDA approved and considered interchangeable. Patients may start receiving azacitidine by one route and changed to the other, and also administration schedules from one schedule and changed to the other at any time as needed based on patient and/or physician preference.
- Avelumab infusion at a dose of 10 mg/kg (maximum dose: 2000 mg) should begin 30-60 minutes after the completion of azacitidine on day 1, as described above, whenever possible. A second dose of avelumab will be administered on Day 14 of each 28 day cycle. Premedication with an antihistamine and with paracetamol (acetaminophen) (for example, 25-50 mg diphenhydramine and 500-650 mg paracetamol [acetaminophen] IV or oral equivalent) is mandatory and recommended approximately 30 to 60 minutes prior to each dose of avelumab. This regimen may be modified based on local treatment standards and guidelines as appropriate provided it does not include systemic corticosteroids.
- PF-04518600 will be administered 30-60 minutes after completion of the avelumab infusion in absence of infusion reaction on Days 1 and 14 (+/-2 days) of each 28 day cycle. Specifics of drug administration and premedications will be the same as specified in Arm A.
- Following completion of the infusions, it is recommended to observe patients for 2 hours post-infusion for potential infusion-related reactions. The ambulatory treatment center/inpatient nurse will use the institutional flowsheet to document observation of the patient as per institutional standards.

(F) Arm F (GO + Glasdegib in RR AML): N= Up to 21

- **The recommended starting dose of GO in this arm is 3 mg/m^2 on Days 1, 4 and 7.** In order to mitigate potential toxicity, the dose may be capped at 4.5 mg at the discretion of the treating physician. GO will not be administered for a longer duration or repeated beyond the Day 1, 4, 7 dosing. The GO solution, following reconstitution and dilution in saline, can be infused to deliver the dose over a 2-hour period on Days 1, 4, and 7. During the infusion, only the syringe or IV bag needs to be protected from light. GO should never be administered as an IV push or bolus. Prevention and monitoring of infusion reactions and tumor lysis syndrome and monitoring for VOD and hold parameters will be as outlined in Arm B.
- Glasdegib will be administered as a 100 mg PO qday to be taken continuously. Glasdegib will be self-administered by the patient at home, unless otherwise specified. Glasdegib, starting dose of 100mg, will be administered orally with approximately 8 ounces (240 mL) of water and should be taken in the morning, at the same time each day. Tablets must not be crushed or cut; they must be swallowed whole, not manipulated or not chewed prior to swallowing. Patients should be instructed to self-administer their medication in the morning at approximately the same time each day and to not take more than the prescribed dose at any time. If a patient forgets to take their dose at the regularly scheduled

time, and if less than 10 hours have passed since the scheduled dosing time, that dose should be taken as soon as possible. If more than 10 hours have passed since the scheduled dosing time, the dose should be skipped and the patient should continue on their normal dosing schedule. If a patient misses a day's dose entirely, they must be instructed not to "make it up" the next day. If a patient vomits any time after taking a dose, they must be instructed not to "make it up," but to resume subsequent doses the next day as prescribed. If a patient inadvertently takes 1 extra dose during a day, the patient should not take the next dose of glasdegib.

- Patients requiring glasdegib dose reduction(s) will be administered multiples of 25 mg tablets and should continue taking the glasdegib at the same time each morning at the dose prescribed by the Investigator (i.e., 75 mg QD and 50 mg QD in the form of three or two 25 mg tablets respectively). In situations where clinical benefit is observed, glasdegib can be reduced below 50 mg QD upon Sponsor approval.
- Glasdegib (PF-04449913) will be supplied in strengths of 25mg and 100mg tablets. Both strengths will be packaged in bottles of 34 tablets. Full bottles of glasdegib will be dispensed to the patient.

5.3 TREATMENT CYCLES

- One cycle of therapy is defined as 28 days (+/- 4 days). Patients will receive one cycle of therapy every 28 days (+/- 4 days).

- Cycles may be started early (but not earlier than day 24) for patients with active disease if judged in the best interest of the patient.
  For the dose finding PF-04518600 monotherapy cohort, the DLT defining period is 28 days. As such, cycle 2 should not be commenced before 28 days for the patients being treated in the lead-in cohort.

- Subsequent cycles may be delayed for recovery of toxicity or other medical conditions (e.g. infections). Delays in the start of subsequent cycles greater than 8 weeks will be acceptable only for patients who are deriving clinical benefit and after discussion with the principal investigator of potential risk/benefit ratio and clear documentation in the medical record of the reason for continuation and perceived benefit to the patient from continuation of this therapy.

- In instances where one drug has to be discontinued transiently because of safety, the administration of the other drug/s may continue as scheduled.

- Therapy will be held during phase II of the study, for grade 4 neutropenia or grade 4 thrombocytopenia lasting ≥ 42 days from the start of each cycle, in the absence of any evidence of active AML in the bone marrow or peripheral blood. Delays in start of subsequent cycles greater than 42 days will be acceptable only for patients who are deriving clinical benefit and after discussion with the principal investigator of potential risk/benefit ratio.

- If the peripheral counts do not recover (ANC $<0.5 \times 10^9$/L and/or platelets $<25 \times 10^9$/L) but there is evidence of residual leukemia by morphology or flow-cytometry in the bone marrow, subsequent cycles can be administered at the discretion of the treating physician not earlier than 24 days after the prior cycle in

the phase II portion of the study.

- For patients who discontinue therapy, the reason for treatment discontinuation will be captured.

5.4 DOSE ADJUSTMENTS

5.4.1 Dose adjustments for hematological drug- related adverse events (AE):

- Dose reduction/interruption/discontinuation decisions should be based on the CTCAE version 4.03 (**Appendix**) and the guidelines provided below.

  Patients with acute leukemias usually present with abnormal peripheral blood counts at the time therapy is started, and myelosuppression is an expected event during the course of therapy for acute leukemia. Thus, no dose adjustments or treatment interruptions for myelosuppression will be planned for the first 4 cycles in patients in whom myelosuppression is due to the presence of residual leukemia. After cycle 1, treatment interruptions and dose adjustments may be considered according to the following guidelines when there is no evidence of active leukemia (e.g., only if <5% blasts in the bone marrow or cytopenias not considered to be related to leukemia).

  ➢ Patients with a response (no evidence of any residual leukemia on bone marrow and/or peripheral blood) and pre-cycle counts of neutrophils >1x10^9/L and platelets >50 x10^9/L will have dose modifications for hematological toxicities as specified in the azacitidine and gemtuzumab PIs and the venetoclax, avelumab, PF-04518600, and glasdegib IBs (Appendix) .

  ➢ If there are persistent peripheral blood blasts, or the bone marrow shows >5% blasts or any evidence of residual leukemia, treatment may be continued regardless of neutrophil and platelet count with supportive care as needed. Dose-interruptions of individual drugs in these patients should be considered on an individual case-by-case basis and discussed with the PI.

  ➢ Investigators should, whenever possible, determine which medication is causing the toxicity and interrupt or dose reduce, as applicable. No dose reductions (only dose interruptions as needed) are permitted for the IO-agents (avelumab and PF-04518600) in the phase II portion.

  - Patients who are experiencing ongoing dose delays >8 weeks due to unresolved grade ≥3 adverse events should be taken off treatment.

5.4.2 Dose adjustments for non-hematologic drug- related AEs

Investigators should, whenever possible, determine which medication is causing the toxicity and interrupt or dose reduce azacitidine, venetoclax, glasdegib, GO and/or interrupt IO-agents, as applicable (Table 3). No dose reductions (only interruptions) are permitted for the IO-agents (avelumab and **PF-04518600**) in the phase II portion.

Dose reductions of azacitidine will be as follows: dose level -1 of azacitidine: 50 mg/m^2 x 7 days, dose level -2: 37.5 mg/m^2 x 7 days, dose level -3: 25 mg/m^2 x 7 days. Further reductions beyond what is shown above or alternative reductions (e.g. 75mg/m2 x 5 days) may be allowed if deemed in the patient's best interest by the treating physician.

Dose reductions of venetoclax will be as follows: dose level -1 of venetoclax: 200mg, dose level -2: 100mg, dose level -3, 50mg. Alternatively, the duration of venetoclax administration can be decreased (e.g. decrease from 21-day to 14-day administration) rather the dose being reduced.

The dose of GO is 3mg/m^2 and dose-reductions will not be done. In case of toxicity considered to be related to GO the dose/s of GO will be omitted.

Separate dose-modifications for glasdegib are presented in section 5.4.7 and should be followed for toxicities considered to be related to the glasdegib.

Table 3. Dose adjustments of azacitidine for non-hematologic drug-related AEs, clinically significant in the opinion of the investigator

Grade	Occurrence	Dose modification
1 or 2	Any time	No dose reduction
3 or 4 (Persistent grade 2: Consider similar dose adjustments if persistent and not responding to optimal management in the opinion of PI and treating physician)	1st and 2nd time	Hold suspected drug. Resume the held drug at prior dose if recovery to ≤ Grade 1 occurs within 14 days. If toxicity persists for 15-28 days, hold the drug and resume at prior dose if recovery to ≤ Grade 1 OR resume the drug at ONE dose level below current dose if recovery to ≤ Grade 2. Dose re-escalation to prior dose of the drug is permitted in accordance with the dose-escalation guidelines in section 5.4.7.
	3rd.	Hold suspected drug. Follow until toxicity ≤ Grade 2. Resume the held drug at ONE dose level below current dose. Dose re-escalation of the drug to prior dose is permitted in accordance with the dose-escalation guidelines outlined below Patients who are experiencing ongoing dose delays >8 weeks due to unresolved grade ≥3 adverse events should be taken off treatment.
	4th time	Discontinue therapy

5.4.3 IO-agent (avelumab and PF-04518600) dose delay/interruption for immune-oncology drug-related AEs, clinically significant in the opinion of the investigator

All IO-agent/s administration should be delayed for the following drug-related AEs, clinically significant in the opinion of the investigator:
• Any Grade >/=2 non-skin AE, except that
– Grade 2 fatigue or laboratory abnormalities do not require delay, however patients with ALT or AST > 3 and up to 5 x ULN or total bilirubin greater > 2.0 mg/dL and up to 3 x ULN or creatinine >2.0 mg/dL and up to 3 x ULN should have avelumab treatment withheld.

All IO agent/s administration should be delayed for the following drug-related AEs, clinically significant in the opinion of the investigator:
• Any Grade 3 skin AE, or Grade 3 laboratory abnormality, with the following exceptions:
− Grade 3 lymphopenia or leukopenia does not require dose delay.
− However, patients with drug-related ALT or AST >5 x ULN or total bilirubin greater > 3 x ULN or creatinine >3 x ULN should have avelumab treatment interrupted.
• Any AE, laboratory abnormality, or intercurrent illness, which in the judgment of the investigator, warrants delaying the dose of study medication.
• IO-agent dose reductions are not permitted in this study (only dose delays when indicated).

Subjects may resume treatment with study drug when the drug-related AE(s) resolve to Grade ≤1 or baseline value, with the following exceptions:
• Subjects may resume treatment in the presence of Grade 2 drug-related fatigue
• Subjects who have not experienced a Grade 3 drug-related skin AE may resume treatment in the presence of Grade 2 skin toxicity
• Drug-related pulmonary toxicity, diarrhea, or colitis, must have resolved to baseline or at least </= grade 1 before treatment is resumed
• Drug-related endocrinopathies adequately controlled may resume treatment

If the criteria to resume treatment are met, the subject should restart treatment at the next scheduled time point per protocol. However, if the treatment is delayed past the next scheduled time point per protocol, the next scheduled time point will be delayed until dosing resumes. Patients who receive combination therapy in whom continuation of the non-IO agent(s) (e.g azacitidine, GO and/or venetoclax) is considered to be inadequate, or inappropriate (e.g., because of pancytopenia or other considered related severe toxicity) can discontinue these agents and continue with IO-agent only.

Patients who are experiencing ongoing dose delays >8 weeks due to unresolved grade ≥3 adverse events should be taken off treatment, except as specified in discontinuation section.

5.4.4 IO-agent Discontinuation Criteria: The following clinically significant, drug-related ADRs require permanent treatment discontinuation of any IO=agent/s:

---**Any Grade 4 drug-related AEs require treatment discontinuation with IO-agent/s** except for single laboratory values out of normal range that are unlikely related to study treatment as assessed by the Investigator, do not have any clinical correlate, and resolve within 7 days with adequate medical management
---**Any Grade 3 drug-related AEs require treatment discontinuation with IO-agent/s except for any of the following:**

- Transient (≤ 6 hours) Grade 3 flu-like symptoms or fever, which is controlled with medical management

- Transient (≤ 24 hours) Grade 3 fatigue, local reactions, headache, nausea, emesis that resolves to Grade ≤ 1

- Single laboratory values out of normal range (excluding Grade ≥ 3 liver function test increase) that are unlikely related to study treatment according to the Investigator, do not have any clinical correlate, and resolve to Grade ≤ 1 within 7 days with adequate medical management

- Tumor flare phenomenon defined as local pain, irritation, or rash localized at sites of known or suspected tumor

- Change in ECOG PS to ≥ 3 that does not resolve to ≤ 2 within 14 days (infusions should not be given on the following cycle, if the ECOG PS is ≥ 3 on the day of study drug administration)

Any Grade 2 drug-related AEs should be managed as follows:

- If a Grade 2 AE resolves to Grade ≤ 1 by the last day of the current cycle, treatment may continue.

- If a Grade 2 AE does not resolve to Grade ≤ 1 by the last day of the current cycle, infusions should not be given on the following cycle. If at the end of the following cycle the event has not resolved to Grade 1, the subject should permanently discontinue treatment with IO-agent/s (except for hormone insufficiencies, that can be managed by replacement therapy; for these hormone insufficiencies, up to 2 subsequent doses may be omitted).

- Upon the second occurrence of the same Grade 2 AE (except for hormone insufficiencies that can be managed by replacement therapy) in the same subject, treatment with the IO-agent/s has to be permanently discontinued unless the patient is deriving clinical benefit in which case the agent may be continued after discussion with the PI of potential risk/benefit ratio and documentation of this discussion in the patents medical record.

- Infusion-related reactions, hypersensitivity reactions (Grades 1 to 4), and tumor lysis syndrome should be handled according to guidelines provided.

• Any dosing interruption due to drug-related toxicity lasting > 8 weeks

5.4.5 Detailed management algorithms for immune-oncology drug-related adverse events (including gastrointestinal, renal, pulmonary, hepatic, endocrine, skin and neurological) are provided in Table 4 below. These general guidelines constitute guidance to the Investigator and may be supplemented by discussions with the PI and IND Office in specific cases.
Since IO-agent/s stimulates the immune system, immune-related AEs (irAEs) may occur. Treatment of irAEs is mainly dependent upon severity (NCI-CTCAE grade):
Grade 1 to 2: treat symptomatically or with moderate dose steroids, more frequent

monitoring
Grade 1 to 2 (persistent): manage similar to high grade AE (Grade 3 to 4)
Grade 3 to 4: treat with high dose corticosteroids

Table 4. Management of Immune-Related Adverse Events (irAEs) (These are to be followed for toxicities with all immune agents included in this protocol including immune checkpoints and monoclonal antibodies)

Gastrointestinal irAEs		
Severity of Diarrhea / Colitis (NCI-CTCAE v4.03)	**Management**	**Follow-up**
Grade 1 Diarrhea: < 4 stools/day over Baseline Colitis: asymptomatic	Continue IO therapy/s Symptomatic treatment (for example, loperamide)	Close monitoring for worsening symptoms Educate subject to report worsening immediately If worsens: Treat as Grade 2 or 3/4
Grade 2 Diarrhea: 4 to 6 stools per day over Baseline; IV fluids indicated < 24 hours; not interfering with ADL Colitis: abdominal pain; blood in stool	Delay IO therapy/s Symptomatic treatment	If improves to Grade 1: Resume IO-therapy/s If persists > 5 to 7 days or recur: 0.5 to 1.0 mg/kg/day methylprednisolone or equivalent When symptoms improve to Grade 1, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume IO-therapy/s per protocol. If worsens or persists > 3 to 5 days with oral steroids: Treat as Grade 3 to 4
Grade 3 to 4 Diarrhea (Grade 3): ≥ 7 stools per day over Baseline; incontinence; IV fluids ≥ 24 hrs; interfering with ADL Colitis (Grade 3): severe abdominal pain, medical intervention indicated, peritoneal signs Grade 4: life-threatening, perforation	Discontinue IO-therapy/s per protocol 1.0 to 2.0 mg/kg/day methylprednisolone IV or equivalent Add prophylactic antibiotics for opportunistic infections Consider lower endoscopy	If improves: Continue steroids until Grade 1, then taper over at least 1 month If persists > 3 to 5 days, or recurs after improvement: Add infliximab 5 mg/kg (if no contraindication), Note: Infliximab should not be used in cases of perforation or sepsis
Dermatological irAEs		

Grade of Rash (NCI-CTCAE v4.03)	**Management**	**Follow-up**
Grade 1 to 2 Covering ≤ 30% body surface area	Symptomatic therapy (for example, antihistamines, topical steroids) Continue IO-therapy/s	If persists > 1 to 2 weeks or recurs: Consider skin biopsy Delay IO-therapy/s Consider 0.5 to 1.0 mg/kg/day methylprednisolone IV or oral equivalent. Once improving, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume IO-therapy/s If worsens: Treat as Grade 3 to 4
Grade 3 to 4 Covering > 30% body surface area; life threatening consequences	Delay or discontinue IO-therapy/s Consider skin biopsy Dermatology consult 1.0 to 2.0 mg/kg/day methylprednisolone IV or IV equivalent	If improves to Grade 1: Taper steroids over at least 1 month and add prophylactic antibiotics for opportunistic infections Resume IO-therapy/s
Pulmonary irAEs		
Grade of Pneumonitis (NCI-CTCAE v4)	**Management**	**Follow-up**
Grade 1 Radiographic changes only	Consider delay of IO-therapy/s Monitor for symptoms every 2 to 3 days Consider Pulmonary and Infectious Disease consults	Re-image at least every 3 weeks If worsens: Treat as Grade 2 or Grade 3 to 4
Grade 2 Mild to moderate new symptoms	Delay IO-therapy/s Pulmonary and Infectious Disease consults Monitor symptoms daily, consider hospitalization 1.0 mg/kg/day methyl-prednisolone IV or oral equivalent Consider bronchoscopy, lung biopsy	Re-image every 1 to 3 days If improves: When symptoms return to near Baseline, taper steroids over at least 1 month and then resume IO-therapy/s and consider prophylactic antibiotics If not improving after 2 weeks or worsening: Treat as Grade 3 to 4
Grade 3 to 4	Discontinue IO-	If improves to Baseline:

Severe new symptoms; New / worsening hypoxia; life-threatening	therapy/s Hospitalize Pulmonary and Infectious Disease consults 2 to 4 mg/kg/day methylprednisolone IV or IV equivalent Add prophylactic antibiotics for opportunistic infections Consider bronchoscopy, lung biopsy	Taper steroids over at least 6 weeks If not improving after 48 hours or worsening: Add additional immunosuppression (for example, infliximab, cyclophosphamide, IV immunoglobulin, or mycophenolate mofetil)
Hepatic irAEs		
Grade of Liver Test Elevation (NCI-CTCAE v4)	**Management**	**Follow-up**
Grade 1 Grade 1 AST or ALT > ULN to 3.0 x ULN and / or total bilirubin > ULN to 1.5 x ULN	Continue IO-therapy/s	Continue liver function monitoring If worsens: Treat as Grade 2 or 3 to 4
Grade 2 AST or ALT > 3.0 to ≤ 5 x ULN and / or total bilirubin > 1.5 to ≤ 3 x ULN	Delay IO-therapy/s Increase frequency of monitoring to every 3 days	If returns to Baseline: Resume routine monitoring, resume IO-therapy/s If elevations persist > 5 to 7 days or worsen: 0.5 to 1 mg/kg/day methylprednisolone or oral equivalent and when LFT returns to Grade 1 or Baseline, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume IO-therapy/s
Grade 3 to 4 AST or ALT > 5 x ULN and / or total bilirubin > 3 x ULN	Discontinue IO-therapy/s Increase frequency of monitoring to every 1 to 2 days 1.0 to 2.0 mg/kg/day methylprednisolone IV or IV equivalent Add prophylactic antibiotics for opportunistic infections Consult	If returns to Grade 2: Taper steroids over at least 1 month If does not improve in > 3 to 5 days, worsens or rebounds: Add mycophenolate mofetil 1 gram (g) twice daily If no response within an additional 3 to 5 days, consider other immunosuppressants per local guidelines

	gastroenterologist Consider obtaining MRI/CT scan of liver and liver biopsy if clinically warranted	
Endocrine irAEs		
Endocrine Disorder	**Management**	**Follow-up**
Asymptomatic TSH abnormality	Continue IO-therapy/s If TSH < 0.5 x LLN, or TSH > 2 x ULN, or consistently out of range in 2 subsequent measurements: include T4 at subsequent cycles as clinically indicated; consider endocrinology consult	
Symptomatic endocrinopathies	Evaluate endocrine function Consider pituitary scan Symptomatic with abnormal lab / pituitary scan: Delay IO-therapy/s 1 to 2 mg/kg/day methylprednisolone IV or by mouth equivalent Initiate appropriate hormone therapy No abnormal lab / pituitary MRI scan but symptoms persist: Repeat labs in 1 to 3 weeks / MRI in 1 month	If improves (with or without hormone replacement): Taper steroids over at least 1 month and consider prophylactic antibiotics for opportunistic infections Resume IO-therapy/s Subjects with adrenal insufficiency may need to continue steroids with mineralocorticoid component
Suspicion of adrenal crisis (for example, severe dehydration, hypotension, shock out of proportion to current illness)	Delay or discontinue IO-therapy/s Rule out sepsis Stress dose of IV steroids with mineralocorticoid activity IV fluids Consult endocrinologist If adrenal crisis ruled out, then treat as above for symptomatic endocrinopathies	
Cardiac irAEs		
Myocarditis	Management	Follow-up
New onset of cardiac signs or symptoms and / or new laboratory cardiac biomarker elevations (e.g. troponin, CK-MB, BNP) or cardiac imaging abnormalities suggestive of myocarditis.	Withhold IO therapy Hospitalize. In the presence of life threatening cardiac decompensation, consider transfer to a facility experienced in advanced heart failure and arrhythmia	If symptoms improve and immune-mediated etiology is ruled out, re-start IO therapy. If symptoms do not improve/worsen, viral

	management. Cardiology consult to establish etiology and rule-out immune-mediated myocarditis. Guideline based supportive treatment as appropriate per cardiology consult.* Consider myocardial biopsy if recommended per cardiology consult.	myocarditis is excluded, and immune-mediated etiology is suspected or confirmed following cardiology consult, manage as immune-mediated myocarditis.
Immune-mediated myocarditis	Permanently discontinue avelumab. Guideline based supportive treatment as appropriate per cardiology consult.* Methylprednisolone 1-2 mg/kg/day.	Once improving, taper steroids over at least 1 month and add prophylactic antibiotics for opportunistic infections. If no improvement or worsening, consider additional immunosuppressions (e.g. azathioprine, cyclosporine A)

*Local guidelines, or eg. ESC or AHA guidelines
ESC guidelines website:
https://www.escardio.org/Guidelines/Clinical-Practice-Guidelines
AHA guidelines website:
http://professional.heart.org/professional/GuidelinesStatements/searchresults.jsp?q=&y=&t=1001

ADL = activities of daily living; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CT = computed tomography; irAE = immune-related adverse event; IV=intravenous; LFT = liver function test; LLN = lower limit of normal; MRI = magnetic resonance imaging; NCI-CTCAE = National Cancer Institute-Common Terminology Criteria for Adverse Event; T4 = free thyroxine; TSH = thyroid-stimulating hormone; ULN = upper limit of normal.

5.4.6 Venetoclax specific dietary recommendations, concomitant medications and dose adjustments

Patients should not consume grapefruit or grapefruit products, Seville oranges, or Star fruit during treatment with venetoclax due to possible CYP3A mediated metabolic interaction.

Moderate and strong CYP3A inducers and inhibitors are discouraged during venetoclax administraton. If a patient requires use of CYP3A inducers, use with caution. In many instances, such as antifungal prophylaxis with “azole” therapy in neutropenic patients, CYP3A inhibitors are required in AML patients. Venetoclax should be administered at

50% dose reduction in the setting of moderate CYP3A inhibitors (e.g. isavuconazole, ciprofloxacin, diltiazem) and 50-75% dose reduction in the setting of strong CYP3A inhibitors (e.g. posaconazole, voriconazole). The venetoclax dose reduction should continue for the duration of co-administration. In the event the co-administered CYP3A inhibitor is discontinued, the assigned venetoclax dose should be resumed 3 days after discontinuation. During the venetoclax ramp-up, these agents must be held; however, they may be started or resumed 24 hours after the highest planned dose of venetoclax is given, along with the appropriate dose reduction of venetoclax as above.

5.4.7 Glasdegib specific dose adjustments

In the event of significant toxicity, dosing must be interrupted, delayed and/or reduced as outlined below. In the event of multiple toxicities, dose modification should be based on the worst toxicity observed. Patients must be instructed to notify investigators at the first occurrence of any adverse symptom/s.

Dose modifications may occur in three ways:

- Within a cycle: Dosing interruption until adequate recovery followed by dose reduction (if required) of glasdegib during a given treatment cycle.
- Between cycles: The next treatment cycle may be delayed if toxicity from the preceding cycle persists.
- In the next cycle: Dose reduction may be required based on toxicities experienced in the previous cycle.

Dosing Interruptions for glasdegib

Patients experiencing Grade 3 or 4 toxicities potentially attributable to glasdegib should have their glasdegib treatment interrupted regardless of when it occurs in the cycle until the toxicity resolves or returns to baseline or </= grade 1.

Appropriate follow-up assessments should be implemented until adequate recovery (toxicity resolves or returns to baseline or </= grade 1) occurs. The criteria that must be met prior to resuming treatment with glasdegib are described below.

Depending on when the adverse event resolved, treatment interruption may lead to the patient missing all subsequent planned doses of glasdegib within the cycle. If the AE leading to treatment interruption recovers within the same cycle, re-commencement of dosing in that cycle is allowed. Glasdegib doses omitted for toxicity will not be replaced within that cycle (e.g., cycles will not be prolonged beyond the 28 days in order to make up for any missed glasdegib doses during that cycle).

The need for a dose reduction at the time of treatment resumption should be based on the criteria outlined below, unless specifically agreed otherwise following discussion between the treating physician and the PI. If a dose reduction for glasdegib is applied in the same cycle, the patient must return to the clinic to receive a new supply of drug.

In the event of glasdegib treatment interruption for reasons other than treatment-related toxicity (e.g., elective surgery) for a duration >21 days, the details of treatment resumption will be determined in consultation with the PI.

Glasdegib treatment should be interrupted for ANC <100/mm^3 and /or platelets <10,000/mm^3 regardless of when it occurs.

Re-commencement of treatment with glasdegib may not occur until the recovery parameters described in Table 6 below are met.

Patients who are experiencing ongoing dose delays >8 weeks due to unresolved grade ≥3 adverse events should be taken off treatment.

At the time of glasdegib re-initiation the non-hematologic toxicities listed in Table 7 below have returned to baseline or ≤ Grade 1 severity.
If these conditions are met within ≤21 days of dose interruption, glasdegib may be resumed. If these parameters have not been met following >21 days of dose interruption, permanent discontinuation of treatment with glasdegib should be considered.

QTcF Interval Monitoring and Management: Patients should be closely monitored for potential cardiovascular symptoms. Appropriate monitoring should include clinical examinations, vital signs, routine ECGs, and AE monitoring. In case of QTcF prolongation, concomitant conditions such as electrolyte imbalances, hypoxia, or use of medications affecting the QT interval should be ruled out or corrected. In case of clinically significant toxicities, glasdegib administration should be interrupted and the dose reduced as indicated in Table 8 below (Glasdegib Dose Modifications for mean QTcF (mQTcF) Prolongation).

Concomitant administration of glasdegib with moderate/strong CYP3A4/5 inhibitors and drugs with known risk of Torsade de Pointes (TdP) is not recommended due to the potential for drug-drug interaction to prolong the QTcF interval. However, if it is medically necessary for patients to use these medications please refer to Section below for details on required assessments and monitoring procedures.

Investigators must be aware of the QTcF-prolonging potential of all medications that patients on study at their site are taking, and should take appropriate action when clinically indicated. Given the potential for QTcF prolongation, the measurement and immediate correction of electrolyte abnormalities such as potassium and magnesium and of other reversible causes of QTcF prolongation such as hypoxia, are especially important during the study. In the event that the QTcF interval is prolonged beyond 480 ms (CTCAE v.4.03 Grade≥ 2), the protocol glasdegib Dose Modifications for mean QTcF (mQTcF) Prolongation must be referenced and actioned (Table 9). Throughout the study additional ECG and cardiac consultation should be obtained as clinically indicated.

Dose Reductions for glasdegib

Following dosing interruption or cycle delay due to toxicity, the glasdegib dose may need to be reduced when treatment is resumed.
Dose reduction of glasdegib by 1 or if necessary, 2 dose levels will be allowed depending on the type and severity of toxicity encountered. In the specific situations where clinical benefit is observed, glasdegib can be reduced below 50 mg QD upon PI approval. All dose modifications/adjustments must be clearly documented in the patient's notes and CRF.

Table 5: Glasdegib dose reduction schema

Glasdegib dose (mg Qday)
100
75
50
25*

*Note: If clinical benefit is observed, glasdegib may be reduced below 50 mg Qday

following PI approval.

Table 6. Glasdegib dose modification for hematologic toxicities

Toxicity (Platelets and Neutrophils only)	**Glasdegib (PF-04449913)[3]**
Recovery within 14 days from when the next cycle is due to start (corresponding to recovery before or on Day 42 of the current cycle)[1, 2]	No Change
Recovery within 14 days, but within 21 days from when the next cycle is due to start (corresponding to recovery before or on Day 42 and before or/on Day 49 of the current cycle)[1, 2]	**First episode:** decrease by 1 dose level **Second episode:** decrease by 1 dose level **Third episode:** permanently discontinue
No recovery by Day 49 of the current cycle	Permanently discontinue

[1]For patients without reduced baseline counts (defined as ANC≥1,000/mm^3 and platelets ≥50,000/mm^3 prior to the first cycle): **Recovery** is defined as ANC> 500/mm^3 and platelets >20,000/mm^3

[2] For patients with reduced baseline counts (defined as ANC≥1,000/mm^3 OR platelets ≥50,000/mm^3 prior to the first cycle): **Recovery** is defined as: reaching at least 50% of cell line(s) counts (where hematological toxicities were observed) of the previous cycle, e.g., if ANC when starting the previous cycle was 800/mm^3, ANC recovery is defined as ANC≥400/mm^3

[3] Glasdegib (PF-04449913) treatment should be interrupted for ANC<100/mm^3 and/or platelets<10,000/mm^3 regardless of when it occurs

Table 7. Glasdegib dose modification for non-hematologic toxicities

Toxicity (NCI CTCAE version 4.03)	**Glasdegib (PF-04449913)**
Renal Toxicity	
Serum creatinine or BUN ≥2x above baseline value or serum bicarbonate level <20mmol/L	**First episode:** decrease by 1 dose level **Second episode:** decrease by 1 dose level **Third episode:** permanently discontinue
≥ Grade 3 toxicity (Nausea, vomiting, and/or diarrhea must persist at ≥ Grade 3 (despite maximal appropriate medical therapy) to require dose modification)	**First episode:** decrease by 1 dose level **Second episode:** decrease by 1 dose level **Third episode:** permanently discontinue

Table 8. Glasdegib Toxicity Grading for QTcF Prolongation

CTCAE v 4.03	Grade 1	Grade 2	Grade 3 **	Grade 4
Electrocardiogram QT corrected (QTc) interval prolonged *	450-480msec	481-500msec	≥501 msec at least two separate ECGs	QTc ≥501 or >60 msec from change from baseline and Torsade de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia

* The severity of QTc prolongation assessment is to be done by calculating a mean QT of 3 consecutive ECGs performed approximately 2 minutes (but no longer than 5 minutes) apart by using the Fridericia correction method (mQTcF).
** If mQTcF is ≥501 msec continuous ECG monitoring and cardiology consultation are required.

Table 9: Evaluation and management of QTcF changes with Glasdegib therapy

Category	Requirement	Grade 1	2	3	4
ECG monitoring	Continuous ECG monitoring and cardiology consultation for mQTcF ≥ 501 msec			x	x
Initial PF 04449913/ placebo action	Discontinue and do not re-challenge.				x
	Interrupt treatment		x	x	
	Continue at same level	x			
General management	Assess for and correct electrolyte abnormalities.	x	x	x	x
	Withhold any concomitant medications if possible that may cause QTc prolongation.		x	x	x
Resume PF 04449913/placebo dosing	At prior dose if mQTcF returns to ≤470 msec and to within 20 msec of baseline in 7 days and if no prior dose interruption related to mQTcF prolongation has occurred		x	x	
	At one lower dose level if mQTcF returns to ≤470msec and to within 20 msec of baseline between 7-14 days. and if no prior dose interruption related to mQTcF prolongation has occurred		x	x	
	At one lower dose level if mQTcF returns to ≤470 msec and to within 20 msec of baseline in 14 days if one prior dosing interruption related to mQTcF prolongation has occurred		x		
Management after dose resumed	An ECG should be repeated and mQTcF re-assessed approximately 7 days after PF-04449913/placebo dosing resumption following interruption for a mQTcF prolongation		x	x	
Discontinue PF-04449913/placebo permanently	The mQTcF prolongation does not return to≤470 msec and to within 20 msec of baseline after 14 days		x	x	
	The Grade ≥ 2 mQTcF prolongation recurs after one dose reduction related to mQTcF prolongation		x	x	
	The Grade ≥3 mQTcF prolongation recurs after one prior dosing interruption related to mQTcF prolongation has occurred			x	
	If at any time during the 14 day window that PF 04449913/placebo is stopped due to QTcF prolongation the patient has a confirmed mean QTcF interval >515 msec or becomes symptomatic		x	x	

Table 10

Dose Modifications for PF-04449913/placebo in Case of Drug Class Related AEs

Muscle Spasms or Myalgia	Grade 1	Grade 2	Grade 3
PF-04449913/ Placebo	Continue at same dose level. Administer oral rehydration solutions containing electrolytes.[a] Consider other appropriate interventions (eg, anti-spasmodics) as per institutional guidelines. Evaluate levels of: CK, Vit B6, Vit D, ferritin, transferin and electrolytes (Na, K, Mg, Ca and P).[b] If CK is elevated, evaluate urine and serum myoglobin, CK isoenzymes, and plasma creatinine.	Continue at same dose level. Administer oral re-hydration salts containing electrolytes.[a] Consider other appropriate interventions (eg, anti-spasmodics) as per institutional guidelines. Evaluate levels of: CK, Vit B6, Vit D, ferritin, transferin and electrolytes (Na, K, Mg, Ca and P).[b] If CK is elevated, evaluate urine and serum myoglobin, CK isoenzymes, and plasma creatinine. If event persists, hold dose until resolution to Grade ≤1. Upon resolution, restart at prior dose, or for prolonged muscle spasms, consider reducing dose by one dose level.	Hold dose. Administer oral re-hydration salts containing electrolytes.[a] Consider other appropriate interventions (eg, anti-spasmodics) as per institutional guidelines. Evaluate levels of: CK, Vit B6, Vit D, ferritin, transferin and electrolytes (Na, K, Mg, Ca and P).[b] If CK is elevated, evaluate urine and serum myoglobin, CK isoenzymes, and plasma creatinine. Upon resolution to Grade ≤1, restart study treatment at next lower dose level. If the event does not resolve within 3 weeks to Grade ≤1, at the discretion of the Investigator the dose may be restarted at the next lower dose level or the patient may be permanently discontinued from study treatment.
In the event of alopecia or dysgeusia, investigator discretion should be applied with respect to dose interruption and/or dose reduction of PF-04449913 as preliminary analysis of available clinical data suggests that these events are not dose dependent.			

CYP3A4/5 Inducers: Glasdegib (PF-04449913) metabolism may be induced when taking CYP3A4/5 inducers, resulting in reduced plasma concentrations. The impact of CYP3A4/5 inducers on PF-04449913 pharmacokinetics has not been studied in the clinic. Therefore co-administration of PF-04449913 with any of the following and other moderate/strong CYP3A4/5 inducers is not permitted from study entry until study treatment discontinuation (avasimibe, mitotane, phenytoin, enzalutamide, semagacestat, bosentan, genistein, thioradazine, nafcillin, modafinil, carbamazepine, phenobarbital,

phenytoin, rifampin, rifabutin, rifapentine, St. John's Wort). A comprehensive list of strong CYP3A4/5 inducers is provided in the Appendix.

Selection of concomitant medication with no or minimal **CYP3A4/5 inhibition** potential is recommended. Moderate/strong CYP3A4/5 inhibitors should be used with caution and only if considered medically necessary. If a moderate/strong CYP3A4/5 inhibitor is to be initiated in addition to glasdegib the guidance provided below requiring additional ECG monitoring before, during and after starting the medication, electrolyte monitoring (including correction and re-checking values) and dose modifications for QT prolongation must be followed.
The concomitant administration of glasdegib and drugs with a known risk of Torsade de pointes should be avoided whenever possible. A list of such drugs is provided in the Appendix. Use of these drugs is not recommended unless there are no alternatives. If a TdP drug is to be initiated in addition to glasdegib the guidance provided below requiring additional ECG monitoring before, during and after starting the medication, electrolyte monitoring (including correction and re-checking values) and dose modifications for QT prolongation must be followed.
QT prolonging medications (without a risk of TdP) should be avoided whenever possible. Concomitant administration of multiple moderate/strong CYP3A4/5 inhibitors, TdP drugs, and/or QT prolonging medications (without a risk of TdP) is not recommended and must be discussed with the PI.

The acceptable mean on-treatment upper limit of QTcF interval is 480 msec. If any patient has a mean pre- or post-dose QTcF value >480 msec, please refer to Table '**Dose Modifications for mean QTcF (mQTcF) Prolongation' (Table 9)** for detailed instructions on management of QTcF prolongation and handling dose delays and dose modifications for glasdegib.

<u>If a moderate/strong CYP3A4/5 inhibitor or TdP drug will be initiated in addition to Glasdegib (PF-04449913) the following guidance must be followed:</u>

-Prior to the start of a moderate/strong CYP3A4/5 inhibitor or TdP drug:
ECGs pre-glasdegib dose, 1 and 4 hours post-glasdegib dose;
Follow dose modifications for QT prolongation.

-After starting a moderate/strong CYP3A4/5 inhibitor or TdP drug: ECGs on Day 2 or 3 and on Day 5, 6, or 7:

-Perform additional ECG testing as appropriate;

- Perform routine electrolyte monitoring (Ca, K, Cl, Mg), implement timely electrolyte correction, followed by appropriate re-checking of values.

When there is an urgent need to start a moderate/strong CYP3A4/5 inhibitor or TdP drug, administration of these medications should not be delayed, the Investigator should consider temporarily interrupting glasdegib dosing and should implement these additional monitoring procedures as soon as it is reasonably possible.

5.4.7 Modifications of dose schedules other than the above will be allowed within the following guidelines:

5.4.7.1 Dose adjustments by more than 1 dose level at a time for azacitidine, venetoclax or glasdegib (e.g., from azacitidine 75 mg/m2 to 25 mg/m2) can be considered when judged in the best interest of the patient (e.g. severe myelosuppression) when toxicity has resolved. The reason for this reduction will be discussed with the PI or Co-PI and documented in the medical record.

5.4.7.2 A patient who has had a dose reduction because of any of the reasons mentioned above may have their dose escalated provided the patient has remained free of toxicity requiring dose adjustments as defined above for at least 1 month. Escalation will be made by 1 dose-level increment only, and not more frequent than every month. The dose of any agent must not exceed the RP2D dose for that agent in this protocol (i.e. azacytidine dose cannot exceed 75mg/m2 x 7 days, venetoclax dose cannot exceed 400 mg/day, and glasdegib dose cannot exceed 100 mg/day).

5.4.7.3 Treatment interruptions and dose modifications other than the ones mentioned above can be considered after discussion with the PI and proper documentation of the rationale. Dose adjustment/delay of only one of the agents is permissible if the toxicity is most likely judged to be related to one of the agents by the investigator (e.g., in patients with autoimmune thyroiditis or autoimmune hepatitis this would be likely secondary to avelumab or PF-04518600, in patients with cytopenias this would be likely secondary to azacitidine and venetoclax, in patients with hepatic congestion or transaminitis this may be secondary to the GO).

5.4.8 Duration of Therapy

In the absence of treatment delays due to adverse events, treatment may continue until one of the following criteria applies:

1. Clinically significant progressive disease, or
2. Intercurrent illness that prevents further administration of either treatment agent, or
3. Patient request, or
4. General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator, or
5. Unacceptable toxicity that in the opinion of the investigator makes it unsafe to continue therapy.

It is planned that up to a total of 24 cycles of therapy will be administered for patients deriving benefit from this regimen. Continuation of therapy for patients completing 24 cycles of therapy may be considered on a case- by-case basis after discussion with the principal investigator and IND Office.

All patients receiving at least one dose of any of the two/three drugs to be received in the combination will be considered evaluable for toxicity and efficacy by intent-to-treat analysis.

5.5 Supportive Care:

Management Algorithms for Treatment of immuno-oncology agents Related Adverse Events Immuno-oncology (I-O) agents are associated with AEs that can differ in severity and duration than AEs caused by other therapeutic classes. Avelumab and PF-04518600 are considered an immuno-oncology agent in this protocol. Early recognition and management of AEs associated with immuno-oncology agents may mitigate severe toxicity. These IO-agent/s has a known safety profile however, a general principle is that differential diagnoses should be diligently evaluated according to standard medical practice. Non- inflammatory etiologies should be considered and appropriately treated. Corticosteroids are a primary therapy for immuno-oncology drug-related adverse events, and avelumab is no exception. The oral equivalent of the recommended IV doses may be considered for ambulatory patients with low-grade toxicities. The lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids. In cases with slightest suspicion of IO-toxicities it is encouraged that the treating physician consult the PI/Co-PI or immunotherapy expert in the department as soon as possible.

Management Algorithms have been developed to assist investigators in assessing and managing the following groups of adverse events: Endocrinopathies, Gastrointestinal, Hepatic, Neurological Pulmonary, Renal and Skin. These algorithms are found in the "Avelumab and PF-04518600 Investigator Brochures" (Appendix) and "Table 4-Management of immune related adverse events" of this protocol. The guidance provided in these algorithms should not replace the Investigator's medical judgment but should complement it.

Finally, consultation with a medical or surgical specialist, especially prior to an invasive diagnostic or therapeutic procedure, is highly recommended.

5.6 Concomitant Medications

Supportive care measures including blood products, infection prophylaxis and growth factors will be administered according to institutional and MDACC Leukemia Department guidelines (Table 11).

Table 11: Instructions for the use of concomitant medications and therapies

Category of Use	Medication	Comment on Use	Restriction on Use
Recommended	Prophylactic antibiotics, antifungal agents, and antiviral agents	Strongly encouraged	None
	Antiemetic agents	According to standard of care at MDACC	None
Allowed	Oral allopurinol or rasburicase	At investigators discretion	None
	Leukapheresis	According to standard of care at MDACC	Before induction 1 day 1 only

Category of Use	Medication	Comment on Use	Restriction on Use
	Red blood cell transfusion	None	None
	Platelet transfusion	None	None
	White blood cell transfusion	At investigators discretion according to standard of care at MDACC	None
	Myeloid growth factors or platelet growth factor	At investigators discretion according to standard of care at MDACC	None
	Erythropoietin or darbepoetin	At investigators discretion according to standard of care at MDACC	None
	Any other medication for supportive care	At investigators discretion according to standard of care at MDACC	None
	CYP3A4 inducers, inhibitors in patients on venetoclax or glasdegib, TdP drugs, QT prolonging drugs in patients on glasdegib	Please see section 5.5.6 and 5.4.7 for guidelines on use of these agents	

Consistent with subject safety and comfort, administration of any prescription or over-the-counter drug products other than study medication should be minimized during the study period. Subjects should be discouraged from use of street drugs, herbal remedies, self-prescribed drugs, tobacco products, or excessive alcohol during the clinical study.

If considered necessary for the subject's wellbeing, drugs for concomitant medical conditions or for symptom management may be given at the discretion of the

investigator. The investigator's decision to authorize the use of any drug other than study drug should take into account subject safety, the medical need, the potential for drug interactions, the possibility for masking symptoms of a more significant underlying event, and whether use of the drug will compromise the outcome or integrity of the study.

Subjects should be instructed about the importance of the need to inform the clinic staff of the use of any drugs or remedies (whether prescribed, over-the- counter, or illicit) before and during the course of the study.

Recommendations with regard to specific types of concomitant therapies, supportive care; diet and other interventions are as follows:

Concomitant medications are recommended as prophylaxis for nausea, vomiting, and infections, and are allowed for managing myelosuppression as shown in Table 3. Myelosuppression is expected in patients with AML due to underlying disease, as well as due to chemotherapy (such as azacitidine), or both. Most patients have neutropenia, thrombocytopenia, or both at study entry. Significant or life-threatening myelosuppression may be managed with growth factor support and blood transfusion according to institutional standard of care, American Society of Clinical Oncology (ASCO) Practice Guidelines, and/or NCCN Practice Guidelines.

Infections secondary to myelosuppression are common in patients with AML, and may be related to underlying disease, chemotherapy, or both. Therefore, the use of prophylactic antibiotics, antifungal agents, and antiviral agents is recommended according to institutional standards.

Since the effect of IO-agents, azacitidine, smoothened inhibition may be delayed, patients with high WBC counts may receive hydroxyurea prior to study entry. Hydroxyurea is allowed before the start of study therapy and during the study treatment. Hydroxyurea use would be recorded in the case report form (CRF). Concurrent therapy for CNS prophylaxis or continuation of therapy for controlled CNS disease is permitted. With the exception of these agents, concomitant systemic chemotherapy or radiation therapy is not permitted. Subjects are not allowed to participate concurrently in any other therapeutic clinical study to treat the underlying disease but are eligible to enroll on supportive care clinical trials.

Subjects may be receiving systemic corticosteroids (daily doses ≤10 mg of prednisone or equivalent if indicated for adrenal replacement or antiemetic therapy), topical, or inhaled corticosteroids at study enrollment. They may receive systemic, topical, inhaled, or enteric corticosteroids while on study without limitation if they develop conditions that require corticosteroid therapy; such subjects are not required to discontinue study participation.

All ongoing medications and therapies (including herbal products, nutritional supplements, and nontraditional medications) at screening will be considered prior medications. Concomitant medication data will not be collected or entered into the case report form other than hydroxyurea as mentioned above; however, the subject's medication record will contain a list of concomitant medications. If a prohibited medication is inadvertently administered/ taken by the patient, the patient may remain on study as long as the prohibited medication is discontinued as soon as feasible. If a prohibited medication is considered essential for the patient well being, continuation on

study with concomitant administration of such medication(s) will need to be discussed with and approved by the principal investigator and medical monitor

6.0 DRUG ADMINISTRATION

6.1 IO-agent Patient Monitoring During Infusion (avelumab and PF-04518600)

Vitals should be checked prior to dosing, at least once during infusion, and at least once after completion of infusion.

6.2 Treatment of IO-agent/s Related Infusion Reactions

Since avelumab and PF-04518600 contains only human immunoglobulin protein sequences, they are unlikely to be immunogenic and induce infusion or hypersensitivity reactions. However, if such a reaction were to occur, it might manifest with fever, chills, rigors, headache, rash, pruritus, arthralgias, hypo- or hypertension, bronchospasm, or other symptoms. All Grade 3 or 4 infusion reactions should be reported within 5 days to the Pfizer Medical Monitor and reported as an SAE if criteria are met. Infusion reactions should be graded according to NCI CTCAE (version 4.03) guidelines.

Treatment recommendations for IO-agent related infusion reactions, including severe hypersensitivity reactions and tumor lysis syndrome (TLS) are provided below and may be modified based on MD Anderson treatment standards and guidelines, as appropriate:

A. IO-agent Infusion Related Reactions

Symptoms

- Fever
- Chills
- Rigors
- Diaphoresis
- Headache

Table 12. Treatment Modification for Symptoms of Infusion-Related Reactions

NCI-CTCAE Grade	Treatment Modification for Study Drug
Grade 1 – mild Mild transient reaction; infusion interruption not indicated; intervention not indicated.	Decrease the study drug infusion rate by 50% and monitor closely for any worsening. The total infusion time for study drug should not exceed 120 minutes.
Grade 2 – moderate Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (for example, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤ 24 h.	Stop study drug infusion. Resume infusion at 50% of previous rate once infusion-related reaction has resolved or decreased to at least Grade 1 in severity, and monitor closely for any worsening.
Grade 3 or Grade 4 – severe or life-threatening Grade 3: Prolonged (for example, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae. Grade 4: Life-threatening consequences; urgent intervention indicated.	Stop the study drug infusion immediately and disconnect infusion tubing from the subject. Subjects have to be withdrawn immediately from study drug treatment and must not receive any further study drug treatment.
- Once the infusion rate has been decreased by 50% or interrupted due to an infusion-related reaction, it must remain decreased for all subsequent infusions. - If the subject has a second infusion-related reaction Grade ≥ 2 on the slower infusion rate, the infusion should be stopped and the subject should be removed from study treatment unless the patient is deriving clinical benefit in which the agent may be continued after discussion with the PI of potential risk/benefit ratio and documentation of this discussion in the patents medical record. - If hypersensitivity reaction occurs, the subject must be treated according to the best available medical practice.	

IV = intravenous; NCI-CTCAE = National Cancer Institute-Common Terminology Criteria for Adverse Event; NSAIDs = nonsteroidal anti-inflammatory drugs.

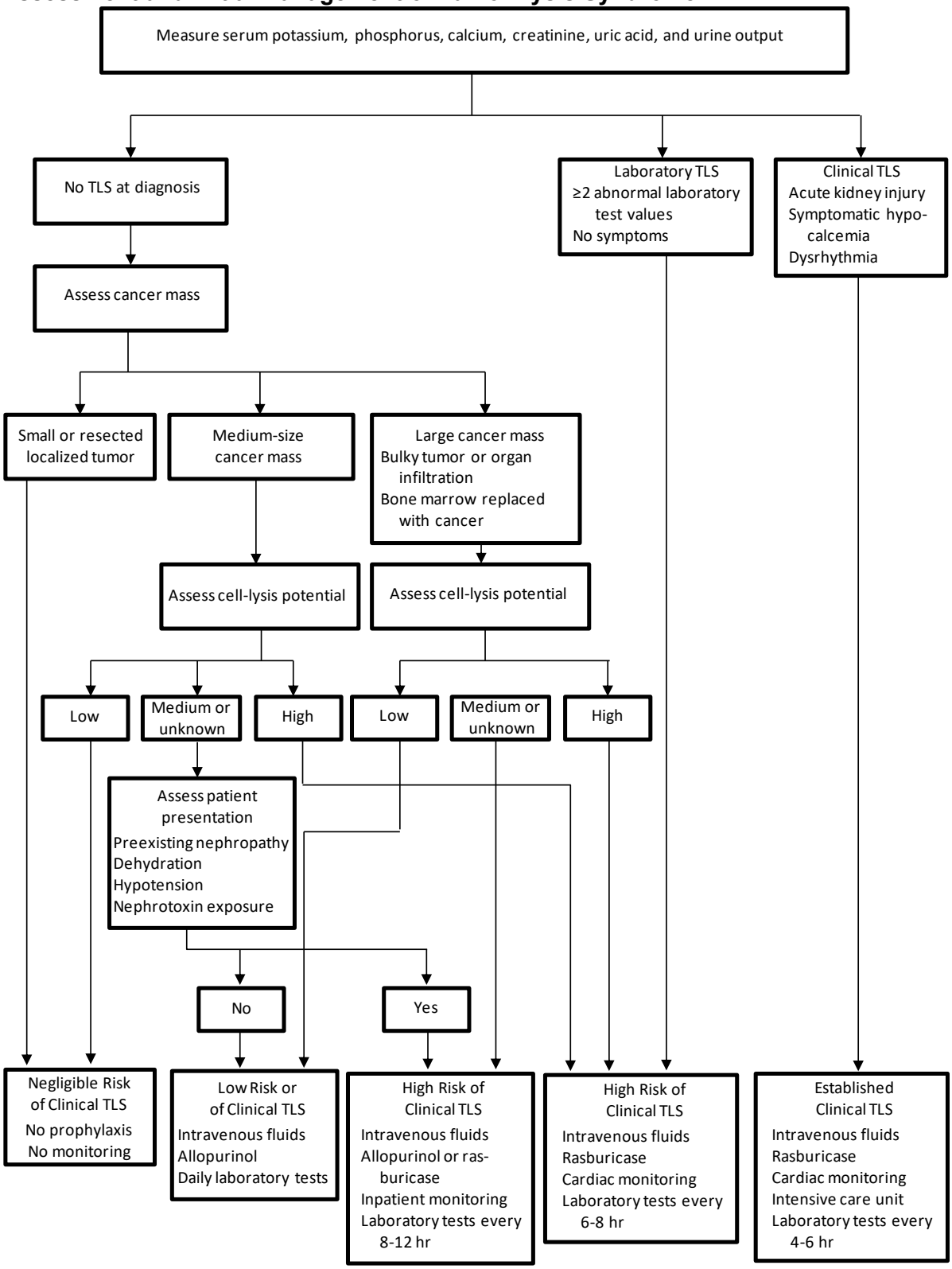
B. Severe Hypersensitivity Reactions and Flu-Like Symptoms

If hypersensitivity reaction occurs, the subject must be treated according to the best available medical practice. Subjects should be instructed to report any delayed reactions to the Investigator immediately.

C. Tumor Lysis Syndrome

In addition, since IO-agents can induce antibody-dependent cell-mediated cytotoxicity, there is a potential risk of tumor lysis syndrome. Should this occur, subjects should be treated per the local guidelines and the management algorithm below (Howard 2011).

Assessment and Initial Management of Tumor Lysis Syndrome



TLS = tumor lysis syndrome

6.3 Azacitidine:
Azacitidine will be commercially obtained. Refer to azacitidine prescribing information (Appendix) in addition to institutional standards for preparation and administration azacitidine.

6.4 GO (Mylotarg)
Infusion reactions (e.g., fever, chills, flushing, hypotension, and dyspnea) have been very commonly encountered in association with GO administration and anaphylaxis has also been reported. Therefore, GO should only be administered in a location that is equipped to manage serious allergic reactions. The possibility of infusion reactions and anaphylaxis should always be anticipated during GO infusions and standard agents for the treatment of allergic/anaphylactic reaction should be available (e.g., oxygen, bronchodilators, intravenous saline, and emergency drugs including epinephrine [adrenaline], diphenhydramine or chlorpheniramine, and methylprednisolone).

Treatment of GO Infusion-Related Reactions (including Anaphylaxis):
GO administration can result in severe hypersensitivity reactions (including anaphylaxis), and other infusion-related reactions which may include severe respiratory symptoms. Infrequently, hypersensitivity reactions and associated pulmonary events have been fatal.

A post-infusion reaction symptom complex of fever and chills, and less commonly hypotension and dyspnea, has been very commonly reported following GO administration, with symptoms typically occurring during, or in the first 24 hours after infusion. The most commonly reported Grade 3 or 4 non-hematologic infusion-related AEs include fever, chills, nausea, vomiting, dyspnea, headache, hyperglycemia, hypertension, hypotension, and hypoxia. Infusion-related symptoms generally resolve after 2 to 4 hours with supportive therapy of acetaminophen, diphenhydramine, and IV fluids. Fewer infusion-related events have been observed after the second dose than after the first dose of GO.

Severe pulmonary events (including pulmonary infiltrates, pleural effusions, non-cardiogenic pulmonary edema, pulmonary insufficiency, and acute respiratory distress syndrome), which may be fatal, have been reported infrequently as part of infusion-related reactions with the use of GO. Patients with an initial WBC count > 30,000/µL may be at increased risk of developing these symptoms and physicians should therefore consider leukoreduction with hydroxyurea or leukapheresis to reduce the peripheral WBC count to < 30,000/µL prior to administration of GO. Patients with symptomatic intrinsic lung disease may also be at increased risk of developing severe pulmonary reactions.

Most patients have received prophylactic diphenhydramine 50 mg orally (PO) or IV and acetaminophen 650 to 1000 mg PO before administration of GO and thereafter, 2 additional doses of acetaminophen 650 to 1000 mg PO, 1 every 4 hours, and additional diphenhydramine may have been administered if required. Methylprednisolone administered prior to GO infusion may further ameliorate infusion-related symptoms. For first infusion, vital signs should be checked prior to the infusion, every 15 minutes (+/- 10 minutes) during infusion, at end of infusion (+/- 10 minutes) and 60 minutes (+/- 30 minutes) after end of infusion. For subsequent infusions, vital signs should be checked prior to the infusion, every 30 minutes (+/- 15 minutes) during infusion, at end of infusion

(+/- 10 minutes) and 60 minutes (+/- 30 minutes) after end of infusion..

GO infusion should be interrupted for patients experiencing dyspnea or clinically significant hypotension, fever or chills and patients monitored until signs and symptoms completely resolve. Once symptoms have resolved, reinfusion at a lower rate (e.g., 50% slower) could be attempted but permanent discontinuation of treatment with GO should be strongly considered for patients who develop anaphylaxis, pulmonary edema, or acute respiratory distress syndrome. Since patients with high peripheral blast counts may be at greater risk for infusion-related pulmonary events, physicians should consider leukoreduction with hydroxyurea or leukapheresis to reduce the peripheral WBC count to below 30,000/μL prior to administration of GO.

6.5 Venetoclax will be commercially obtained. Refer to venetoclax Prescribing Label (Appendix).

6.6 Variations in infusion times of drugs due to minor differences in IV bag overfill/under fill and institutional procedure on flushing chemotherapy lines will not result in protocol deviation. All infusion times are considered approximate.

6.7 Unused or expired drugs will be safely disposed according to MD Anderson pharmacy standard guidelines.

6.8 For further details on drug formulation, reconstitution, administration, infusion related instructions, concern and plan of management for infusion related topics please the respective agents IB and/or Pharmacy Manuals (Appendices)

7.0 PATIENT EVALUATION

Every effort will be made to adhere to the schedule of events and all protocol requirements. Variations in schedule of events and other protocol requirements that do not affect the rights and safety of the patient will not be considered as deviations. Such variations may include laboratory assessments completed outside of schedule, occasional missed required research samples such as correlative assays.

7.1 Pre-Treatment Evaluation

All pretreatment studies should be obtained within 14 days of entry into any of the study arms, unless otherwise stated.

7.1.1 A complete history and physical, documentation of all measurable disease, concomitant medications and performance status.

7.1.2 CBC, platelet count, differential (differential can be omitted if WBC is ≤0.5 $x10^9$/L).

7.1.3 Creatinine, total bilirubin, ALT or AST, electrolytes, glucose, uric acid, creatinine, direct bilirubin, calcium, magnesium, alkaline phosphatase, BUN.

7.1.4 Pregnancy test (urine or plasma) in females of childbearing potential should be performed within 72 hours before initiation of protocol therapy.

7.1.5 Bone marrow aspirate during the last 28 days (+/- 7 days) preceding study initiation. Cytogenetics will be obtained prior to therapy (results from prior analysis can be used for this purpose).

7.1.6 Electrocardiogram EKG at baseline. Cardiac ECHO or MUGA at baseline. Troponin-T, CK, CK-MB, NT-proBNP at baseline

7.1.7 Urine for routine urine analysis

7.1.8 TSH, total T3, free T4, serum fasting cortisol, testosterone (in males), growth hormone level: GnRHs

7.1.9 Chest X-Ray PA/Lateral

7.1.10 Nasal wash for viral PCR

7.1.11 Pretreatment optional correlative studies (see below)

7.2 Evaluation During Treatment

7.2.1 Physical exam at the start of each cycle (± 4 days).

7.2.2 CBC, platelet count, differential two times per week (+/- 4days) for the first 3 cycles, then one to two times per week (+/- 4 days) in subsequent cycles (differential can be omitted if WBC is ≤0.5 $x10^9$/L)

7.2.3 Creatinine, total bilirubin, ALT, or AST, electrolytes, glucose, uric acid, creatinine, direct bilirubin, calcium, magnesium, alkaline phosphatase, BUN two times per week (+/- 4 days) for the first 3 cycles, then one to two times per week (+/- 4 days) in subsequent cycles

7.2.4 In venetoclax containing arms only (Arms B and D): TLS chemistry tests (potassium, uric acid, creatinine, calcium and phosphorus) will be obtained daily prior to dosing and 6-8 hours on each day after a new venetoclax dose during cycle 1

7.2.5 Cortisol, TSH, Total T3, Free T4 once every cycle for the first 3 cycles, then once every 3 months.

7.2.6 Troponin-T, CK, CKMB and NT-proBNP once every cycle for patients on glasdegib-containing arms.

7.2.7 EKG on Day 1 of each cycle of therapy for patients on glasdegib-containing arms.

7.2.8 ECHO or MUGA after every 3 cycles of therapy.

7.2.9 Urinalysis day 1 of every cycle

7.2.10 Bone marrow aspiration on day 28 (+/- 4 days), then on day 28 (+/- 4 days) of cycles 2, 4, 8 and progression. Bone marrow tests can be ordered more frequently if mandated by development of peripheral blood counts. No repeat bone marrow is necessary if nonresponse or progressive disease can be unequivocally diagnosed from peripheral blood tests or, in patients with a WBC < 0.3 if the bone marrow test is considered noncontributory by the investigator at any time point. Bone marrow examinations can be omitted at the discretion of PI and co-PI in patients with no bone marrow involvement at the time of screening. Response assessment should be instead performed with appropriate imaging (e.g. PET CT) as determined by the treating physician, depending on the site of disease.

7.2.11 In venetoclax containing arms only (Arms B and D): Bone marrow aspiration will also be performed on day 21 (+/- 3 days) of cycle 1 and follow the guidelines in section 5.

7.2.12 Concomitant medication data will not be collected or entered into the case report form except for concomitant hydroxyurea; however, the subject's medication record will contain a list of concomitant medications.

7.2.13 **Correlative Studies relating to immunologic response (Optional):** Tumor tissue, blood samples and bone marrow aspirate for correlative research will be collected in patients who consent to participate in the optional procedures. Correlative laboratory studies will be conducted under this clinical trial as described: Patients may participate in the clinical study protocol irrespective of whether they choose to participate in the correlative studies. In tumor tissues, immunohistochemical studies will be performed to evaluate tumor and immunological cell markers such as CD4 and CD8 T cells. In peripheral blood, we will also evaluate tumor and immune cell populations including but not limited to CD4 and CD8 T cells in pre and post therapy samples.

Proposed correlative studies to be performed:

- Standard of Care tests done on all AML patients at MDACC: To analyze for the presence of common somatic mutations, we routinely perform a 53-gene/28-gene panel with validated, next-generation platform sequencing on DNA extracted from bone marrow samples in the CLIA-certified molecular laboratory at MD Anderson Cancer Center at pre-treatment and end of study (if available) assessment for all AML patients at MDACC. Multiparametric flow-cytometry for minimal residual disease (MRD) assessment in AML by validated 15 color flow cytometry, cytogenetics, FISH and molecular markers

(if mutated at baseline) at baseline and on treatment to assess for MRD will be done routinely at MDACC Hematopathology lab as standard of care. These data will automatically be available for all patients and will allow exploration of correlations between specific somatic mutations and/or cytogenetic aberrations and response in AML patients.

- Multi-stain immunohistochemistry and validated immune relevant multiparametric flow-cytometry on bone marrow aspirate (or slides) and peripheral blood at baseline, EOC2, EOC4, progression on all patients to: (a) identify the immunophenotype of tumor-infiltrating T-lymphocytes (TIL): CD8+, CD4+ effector, or CD4+ regulatory, (b) determine the quantitative expression of immune ligands on AML blasts, MSCs and (c) determine the quantitative expression of positive and negative co-stimulatory molecules on TILs pre- and post-therapy with the combination. For the analysis of the co-stimulatory ligands on leukemic blasts (defined as CD13+HLADR+CD33+CD38+), we have developed the "AML tumor ligand panel": 4-1BBL, B7-1, B7-2, ICOSL, PDL-1, PDL-2, OX40L, CD40, CD27L, and CD137L. For the analysis of co-stimulatory molecules on T cells (CD4 T effector cells defined as CD3+CD4+Foxp3- cells; CD4 T regulatory cells defined as CD3+CD4+CD127-Foxp3+ cells, and CD8 T cells defined as CD3+CD8+) we have developed the "AML lymphocyte panel": 4-1BB, CTLA-4, CD28, ICOS, PD-1, OX40, CD40L, LAG-3 and TIM-3. These studies may enable identification of prognostic and predictive markers and enable the identification of other immune checkpoints of significance for future checkpoint based therapeutic approaches in AML. These studies may be performed in the Department of Leukemia and Immunotherapy platform using validated MFC (or Cytof panels that we are currently validating) or through Pfizer commercial vendors depending on the more financially viable option.

- RNA sequencing (Illumina Hi-seq) and Nanostring analysis for IO-gene signature and gene expression for "stemness" associated genes [Ng et al, A 17-gene stemness score for rapid determination of risk in acute leukaemia. Nature. 2016 Dec 15;540(7633):433-437.] on bone marrow aspirate (and possibly on peripheral blood) at baseline, EOC2, EOC4, and at progression

- TCR analysis on bone marrow aspirate and peripheral blood at baseline, EOC2, EOC4, and progression on all patients

- Serum cytokine profiling by ELISA panels at baseline, EOC2, EOC4, and progression on bone marrow aspirate and peripheral blood on all patients.

Peripheral blood up to 40 mL (within 24 hours) will be collected in patients who consent to the correlative studies for testing of biomarkers at the following time points:
-Baseline (prior to day 1 dose of drug), and on day 28 (+/- 4) on cycle 1 (done at MD Anderson), at day 28 (+/- 4 days) of cycles 2, 4, 8.

Bone marrow samples will be collected in patients who consent to the correlative studies for testing of biomarkers at baseline, on day 28, at day 28 (+/- 4 days) of cycles 2, 4, 8, and at progression (if possible).

All correlative samples are optional.

Missed samples for correlative studies will not constitute protocol deviations.

- For patients that remain on study with no significant toxicity for more than 6 months, subsequent evaluations during study may be modified after discussion with the principal investigator. These include a decrease in frequency of bone marrow aspirations to every 6-12 months (or as clinically indicated), correlative studies to every 6-12 months (or suspension of sample collection for correlative studies), other laboratory tests to once every cycle.

- ALL treatments with the investigational agents including PF-04518600, avelumab, GO must be administered at the MDACC outpatient clinic. The first cycle of azacitidine must be administered at the MDACC outpatient clinic, when applicable. Subsequently, patients will have the option of receiving azacitidine injections or infusions at the MDACC outpatient clinic or local ambulatory treatment center. We do not intend for the subjects to receive PF-04518600, avelumab, or GO at any time at an outside physician's office. During the first cycle for ALL arms A-F all the laboratory evaluations will be done at MDACC and the patients must stay locally within easy access of MDACC. Subsequently, the patient may have the laboratory work done at a local clinic and the results reported and filed by the MDACC research nurse for the study. The laboratory work done at the local clinic will be forwarded to the patient's attending physician at MDACC or PI of the study, who will sign off on the labs to verify that the results have been reviewed.

Outside Physician Participation During Treatment

1. MDACC Physician communication with the outside physician is required prior to the patient returning to the local physician. This will be documented in the patient record.
2. A letter to the local physician outlining the patient's participation in a clinical trial will request local physician agreement to supervise the patient's care (**Appendix S**).
3. Protocol required evaluations outside MDACC will be documented by telephone, fax or e-mail. Fax and/or e-mail will be dated and signed by the MDACC physician, indicating that they have reviewed it. Changes in drug dose and/or schedule must be discussed with and approved by the MDACC physician investigator, or they're representative prior to initiation, and will be documented in the patient record.
4. A copy of the informed consent, protocol abstract, treatment schema and evaluation during treatment will be provided to the local physician.
5. Documentation to be provided by the local physician will include progress notes, reports of protocol required laboratory and diagnostic

studies and documentation of any hospitalizations.

6. The home physician will be requested to report to the MDACC physician investigator all life threatening events within 24 hours of documented occurrence.
7. All follow-up visits will be performed at MDACC.
8. Changes in drug dose and/or schedule must be discussed with and approved by the MDACC physician investigator, or they're representative prior to initiation, and will be documented in the patient record.

7.2.14 Patients with an objective response at completion of active study treatment will be followed for survival at MD Anderson Cancer Center (MDACC) every 3 to 6 months for up to 5 years after completion of active treatment and while still on study. If the patient is unable to return to MDACC the follow-up visits may be conducted via telephone.

Table 13. The study assessment schema is shown in tabular form below

Study Period/Cycle	Screening*	Treatment																		End of Study (EOS)[h,i]	Long-Term Follow-Up
		Cycle 1						Cycle 2						Cycle 3					Subsequent Cycles[j]		
Cycle Day		1	8	14	15	22	28	1	8	14	15	22	28	1	8	14	15	22	1	30 Days After Last Dose	Every 3-6 months
Study Day	-14 to 0	1	8		15	22		29	36		43	50		57	64	70	71	78	__		
Complete history	X	X						X						X					X		
Physical examination[a]	X	X						X						X					X	X	
Vital Signs**		X		X				X		X				X		X			X		
Performance status	X	X						X						X					X	X	
Document all measurable disease (if present)	X																				
Concomitant medications[a]	X	X						X						X					X		X
Chest X-ray PA/Lateral	X																				
Nasal Wash PCR	X																				
ECHO/MUGA	X																		Q 3 cycles		
ECG[k]	X	X						X						X					X		
TropI, CK, CK-MB, BNP[k]	X							X						X					X		
CBC with differential[b]	X	X	X		X	X		X	X		X	X		X	X		X	X	X	X	

Sodium, Potassium, Chloride, glucose, uric acid, bicarbonate, BUN, Creatinine, total bilirubin, direct bilirubin, calcium, magnesium, ALT, or AST, alk phos[b]	X	X	X		X	X		X	X		X	X		X	X		X	X	X	X	
Urinalysis	X	X						X						X					X		
Testosterone (males), GnRH	X																				
TSH, total T3, free T4, cortisol[c]	X	X						X						X					X		
Pregnancy test[d]	X																				
Bone marrow aspirate/ biopsy[e]	X						X												X		

Correlative	**Screening**	**Cycle 1**				**Cycle 2**				**Cycle 3**				**Subsequent cycles**	**EOS**
Optional correlatives on blood[f]	X				Day 28				Day 28					Day 28 of cycles 2,4, 8, prog	If possible
Optional correlatives on bone marrow[g]	X				Day 28				Day 28					Day 1 of cycle 2, 4, 8, prog	If possible

[*] Samples collected at screening do not need to be repeated on Day 1 of Cycle 1.

[**] For first infusion of GO, vital signs should be checked prior to the infusion, every 15 minutes (+/- 10 minutes) during infusion, at end of infusion (+/- 10 minutes) and 60 minutes (+/- 30 minutes) after end of infusion. For subsequent infusions of GO, vital signs should be checked prior to the infusion, every 30 minutes (+/- 15 minutes) during infusion, at end of infusion (+/- 10 minutes) and 60 minutes (+/- 30 minutes) after end of infusion. For avelumab and PF-04518600, vitals should be checked prior to dosing, at least once during infusion and at least once after completion of infusion.

[a]A complete physical examination and documentation of concomitant medications will be done on day 1 of each cycle (+/- 4 days).

[b]The specified labs must be done at least twice weekly (+/- 4 days) for the first 3 cycles, then every 2-4 weeks on subsequent cycles. The labs may be done more frequently than twice a week at the discretion of the treating physician and/or the PI. Differential can be omitted if WBC $\leq 0.5 \times 10^9$/L. In venetoclax containing-arms only (Arms B and D), TLS chemistry tests (potassium, uric acid, creatinine, calcium and phosphorus) will be obtained prior to dosing and 6-8 hours on each day after a new venetoclax dose during cycle 1.

[c] Cortisol, TSH, total T3, free T4 will be done at least once monthly (+/- 4 days) after the start of therapy for the first 3 cycles, then every 3 months (+/- 4 days) on subsequent cycles.

[d]Pregnancy test either urine or plasma should be done in women of childbearing potential 72 hours before initiation of protocol therapy.

[e]Bone marrow aspiration must be done within 28-days (+/- 7 days) of initiation of therapy, then Day 28 (+/- 4 days)cycles 2, 4, 8 and progression. Cytogenetics may be used from prior bone marrow analysis if these were not reported on the screening bone marrow. In venetoclax-containing arms only (Arms B and D), bone marrow aspiration should be performed on day 21 (+/- 3 days) of cycle 1. Follow-up bone marrows may be omitted at the discretion of the PI or co-PI for patients with extramedullary disease in whom no bone marrow disease was present at screening.

[f]Correlative studies will be collected on peripheral blood at baseline, 28 on cycle 1. Subsequently, peripheral blood will be obtained on day 28 of cycles 2, 4, and 8. All these tests can be +/- 5 days. Additional samples may be collected if the disease gets worse.

[g]Correlative studies will be collected on bone marrow at baseline, day 28 (+/-4 days), then on day 28 (+/- 4 days) of cycles 4, 8and at progression if possible.

[h]EOS visitis include a physical examination, CBC with differential and platelets and a limited chemistry profile (total bilirubin, serum creatinine, SGPT or SGOT). A bone marrow aspiration may be done if non-response or progressive disease cannot be unequivocally diagnosed from peripheral blood.

[i]Subject will be followed for toxicity for at least 30 days after the last protocol treatment. The 30-day follow-up visit (+ or – 5 days) will be scheduled as a clinic visits for clinical evaluation and physical examinations. If the patient cannot make it to the MDACC clinic for this visit, the required follow up treatment procedures may be done with a local physician and the records forwarded to MDACC. The research nurse will contact the patient by telephone and get a verbal assessment of the patient's condition. The phone conversation will then be documented in the patient's charts.

[j] For patients that remain on study with no significant toxicity for more than 6 months, subsequent evaluations during study may be modified after discussion with the principal investigator. These include a decrease in frequency of bone marrow aspirations to every 6-12 months (or as clinically indicated), correlative studies to every 6-12 months (or suspension of sample collection for correlative studies), other laboratory tests to once every cycle.[k] Perform at specified time-points and repeat as clinically indicated[L] ECG on day 1 of every cycle of therapy

[k] Only for patients on glasdegib-containing arm

Data regarding adverse events will be collected during the study. Protocol specific data will be entered intothe electronic case report form (eCRF). AEs will be recorded in the Case Report Form (eCRF as described under section 10.0).
Treatment may be discontinued for a variety of reasons, including patient withdrawal, investigator decision, and reasons specified by the protocol. Reasons for discontinuation of treatments are described in section 9.0.

8.0 CRITERIA FOR RESPONSE:

Response Criteria for AML

Responses will be assessed by the International Working Group for AML [118].
Responders are patients who obtain a CR, CRp, CRi, or PR, with or without cytogenetic response, hematologic improvements, and morphologic leukemia-free state.

For patients with only extramedullary disease, CR is defined as complete resolution of disease by appropriate imaging. PR is defined as at least 50% reduction of disease by appropriate imaging.

Hematologic Improvement (HI): Hematologic response will be assessed by the MDS IWG response criteria (Cheson et al., Blood 2006)

- Erythroid response (E) (pretreatment Hgb <11 g/dL)
  Hgb increase by >/=1.5 g/dL
- Platelet response (P) (pretreatment platelets <100 x10^9/L)
  Absolute increase of >/=30 x 10^9/L for patients starting with > 20 x 10^9/L platelets
  Increase from < 20 x 10^9/L to > 20 x 10^9/L and by at least 100%
- Neutrophil response (N) (pretreatment ANC <1.0 x10^9/L)
  At least 100% increase and an absolute increase > 0.5 x 10^9/L
- Blast response (B)
  >/=50% reduction in peripheral blood or bone marrow blasts but still >5%

9.0 DISCONTINUATION OF TREATMENT

9.1 Discontinuation Criteria for Individual Patients

9.1.1 Patient Withdrawal
Patients may voluntarily withdraw consent to participate in the clinical study at any time and without giving any reason. Their withdrawal will not jeopardize their relationship with their healthcare providers or affect their future care. Patients may also choose to withdraw from study treatment, but agree to remain in the study for follow-up procedures.

9.1.2 Investigator Discontinuation of Patient

The investigator may exercise medical judgment to discontinue study treatment if clinically significant changes in clinical status or laboratory values are noted.

9.1.3 Criteria for Protocol-Defined Required Discontinuation of Treatment
The protocol requires discontinuation of study treatment for the following reasons:
1. Patient requests discontinuation.
2. Unacceptable toxicity that in the opinion of the investigator makes it unsafe to continue therapy.
3. Clinically significant progressive disease.
4. Investigator discretion.

9.1.4 Follow-Up at Treatment Discontinuation or Early Withdrawal
Patients who discontinue treatment for any reason should complete end-of-treatment procedures when possible. End of treatment procedures will include a physical examination, CBC with differential and platelets and a limited chemistry profile (total bilirubin, serum creatinine, SGPT or SGOT). A bone marrow aspiration may be recommended only if non-response or progressive disease cannot be unequivocally diagnosed from peripheral blood. Although treatment will be discontinued at that time, all patients who do not withdraw consent for follow-up, die, or become lost to follow-up, will remain on study for follow-up evaluations. Subject will be followed for toxicity for at least 100 days after the last protocol treatment. The 100-day follow-up visit (+ or – 5 days) will be scheduled as a clinic visits for clinical evaluation and physical examinations. If the patient cannot make it to the MDACC clinic for this visit, the required follow up treatment procedures may be done with a local physician and the records forwarded to MDACC. The research nurse will contact the patient by telephone and get a verbal assessment of the patient's condition. The phone conversation will then be documented in the patient's charts.

9.2 Study Stopping Rules
The principal investigator and MDACC IND office have the right to terminate this clinical study at any time. The principal investigator and MDACC IND office, as appropriate, will be involved in any decisions regarding terminating the study, temporarily suspending enrollment, or stopping ongoing treatment with study treatment.
Reasons for terminating the clinical study or a study site's participation include, but are not limited to, the following:

- The incidence or severity of an adverse reaction related to treatment in this study or other studies indicates a potential health hazard to patients
- Data recording is significantly inaccurate or incomplete
- Study site personnel are noncompliant with study procedures
- Pattern of noncompliance is observed

9.3 Protocol Violations and Deviations
Protocol violations are defined as significant departures from protocol-required processes or procedures that affect patient safety or benefit potential, or confound assessments of safety or clinical activity. A protocol deviation is a departure from the protocol that does not meet the above criteria. Protocol violations or deviations may be grouped into the following classes:

- Enrollment criteria
- Study activities (missed evaluations or visits) except for those allowed per protocol

- Noncompliance with dose or schedule, including dose calculation, administration, interruption, reduction, or delay; or discontinuation criteria
- Investigational product handling, including storage and accountability
- Informed consent and ethical issues

10.0 ADVERSE EVENT REPORTING

10.1 Monitoring, recording and reporting adverse events

Adverse Event (AE) is any untoward medical occurrence that may present during treatment with a pharmaceutical product but which does not necessarily have a causal relationship with this treatment.

Adverse drug reaction is a response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease or for the modification of physiologic function.

Assessing causal connections between agents and disease is fundamental to the understanding of adverse drug reactions. In general, a drug may be considered a contributory cause of an adverse event if, had the drug not been administered, 1) the event would not have happened at all, 2) the event would have occurred later than it actually did, or 3) the event would have been less severe.

All subjects will be monitored for AEs during the study. AEs will be recorded in the subject's source documents from the first dose through 30 days after the last dose. All Grade 1-4 AEs possibly, probably, likely related to study drug(s) will be captured within the eCRF. Grade 3 and 4 AEs will be captured irrespective of relatedness to study drug(s). Hematologic lab abnormalities will not be recorded or reported as adverse except for prolonged myelosuppression as defined by the NCI-CTCAE criteria specific for leukemia, e.g. marrow hypocellularity on day 42 or later (6 weeks) from start of therapy without evidence of leukemia (< 5% blasts), or that results in dose modifications, interruptions or meets the protocol definition of DLT or SAE.

Serious Adverse Events (SAEs) will be captured starting from the date of consent. The Investigator or physician designee is responsible for verifying and providing source documentation for all adverse events and assigning the attribution for each event for all subjects enrolled on the trial. The Principal Investigator will sign and date the AE log per each patient at the completion of each course. Following signature, the AE log will be used as source documentation for the adverse events for attribution.

The Leukemia-specific Adverse Event Recording and Reporting Guidelines will be followed for the recording and reporting of adverse and serious adverse events.

1. Baseline events will be recorded in the medical history section of the case report form and will include the terminology event name, grade,

and start date of the event. The medical history section of the case report form will serve as the source document for baseline events once signed and dated by the principal investigator.

   a. Baseline events are any medical condition, symptom, or clinically significant lab abnormality present before the informed consent is signed
      i. Hematologic laboratory abnormalities will not be recorded as baseline events for patients with acute leukemia, myelodysplastic syndrome, chronic lymphocytic leukemia, or chronic myeloid leukemia in blast phase.
      ii. If exact start date is unknown, month and year or year may be used as the start date of the baseline event.

2. The maximum grade of the adverse event will be captured per course or protocol defined visit date.
3. These adverse events will be recorded in the case report form:
   a. Any grade adverse event that is possibly, probably, or definitely related to the study drug(s).
   b. All serious adverse events regardless of attribution to the study drug(s).
   c. Any grade adverse event regardless of attribution to the study drug(s) that results in any dose modification.
4. Hematologic adverse events will not be recorded or reported for studies in patients with acute leukemia, myelodysplastic syndrome, chronic lymphocytic leukemia, or chronic myeloid leukemia in blast phase except for:
   a. Prolonged myelosuppression as defined by the NCI-CTCAE criteria specific for leukemia, e.g. marrow hypocellularity on day 42 or later (6 weeks) from start of therapy without evidence of leukemia (< 5% blasts), or that results in dose modifications, interruptions or meets the protocol definition of DLT or SAE.
5. Serious adverse events will be reported according to institutional policy.
6. Protocol specific language regarding the recording and reporting of adverse and serious adverse events will be followed in the event of discordance between the protocol and Leukemia-specific adverse event recording and reporting guidelines.

10.2 Serious Adverse Events (SAEs)

An adverse event or suspected adverse reaction is considered “serious” if, in the view of either the investigator or the sponsor, it results in any of the following outcomes:

- Death
- A life-threatening adverse drug experience – any adverse experience that places the patient, in the view of the initial reporter, at immediate risk of death from the adverse experience as it occurred. It does not include an adverse experience that, had it occurred in a more severe form, might have caused death.

- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- A congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse (21 CFR 312.32).

- Important medical events as defined above, may also be considered serious adverse events. Any important medical event can and should be reported as an SAE if deemed appropriate by the Principal Investigator or the IND Office.

10.3 Reporting SAEs to the IND Office and MDACC IRB

- All events occurring during the conduct of a protocol and meeting the definition of a SAE must be reported to the IRB in accordance with the timeframes and procedures outlined in “The University of Texas M. D. Anderson Cancer Center Institutional Review Board Policy for Investigators on Reporting Unanticipated Adverse Events for Drugs and Devices”. Unless stated otherwise in the protocol, all SAEs, expected or unexpected, must be reported to the IND Office, regardless of attribution (within 5 working days of knowledge of the event).

- All life-threatening or fatal events, that are unexpected, and related to the study drug, must have a written report submitted within 24 hours (next working day) of knowledge of the event to the Safety Project Manager in the IND Office.

- Unless otherwise noted, the electronic SAE application (eSAE) will be utilized for safety reporting to the IND Office and MDACC IRB.

- Serious adverse events will be captured from the time of the first protocol-specific intervention, until 30 days after the last dose of drug, unless the participant withdraws consent. Serious adverse events must be followed until clinical recovery is complete and laboratory tests have returned to baseline, progression of the event has stabilized, or there has been acceptable resolution of the event.

- Additionally, any serious adverse events that occur after the 30

day time period that are related to the study treatment must be reported to the IND Office. This may include the development of a secondary malignancy.

10.4 Reporting SAEs to FDA:

- Serious adverse events will be forwarded to FDA by the IND Sponsor (Safety Project Manager IND Office) according to 21 CFR 312.32.

  It is the responsibility of the PI and the research teams to ensure serious adverse events are reported according to the Code of Federal Regulations, Good Clinical Practices, the protocol guidelines, the IND Office guidelines, and Institutional Review Board policy

10.5 Investigator Communications with Pfizer

All Serious Adverse Events must be reported to Pfizer Clinical Trial Department utilizing the provided Pfizer SAE form.

- All SAEs, whether related or unrelated to study drugs and all pregnancies must be reported to Pfizer (by the investigator or designee) within 24 hours.
- All SAEs should be reported via confirmed facsimile (fax) transmission, or scanned and reported via electronic mail to:

  SAE Email Address: USA.AEReporting@pfizer.com
  SAE Fax Number: 1-866-997-8322

11.0 STATISTICAL CONSIDERATIONS

This is an open-label Phase IB/II multi-arm study. The primary objectives are to determine the maximum tolerable dose (MTD) and identify the dose of PF-04518600 (Arm A), and to evaluate the composite complete response (CRc) within 3 months of therapy initiation of the combination therapies: Azacitidine + venetoclax + GO (arm B), Azacitidine + avelumab + GO (arm C), Azacitidine + venetoclax + avelumab (arm D), Azacitidine + avelumab + PF-04518600 (arm E), and GO + glasdegib (arm F), in patients with relapsed/refractory AML. A total of up to 87 patients will be enrolled in the study (arms with up to 24 patients per arm in arms C-D and 30 patients in arm B, in addition to the 4 patients enrolled in arm A and 5 patients enrolled in arm F at the time of closing these two arms.

Dose safety evaluation for Arm A (PF-04518600 alone in RR AML):

The 0.3 mg/kg dose of PF-04518600 will be evaluated as this was the dose selected to move forward from the solid tumor PF-04518600 single agent dose finding study (B0601002, ClinicalTrials.gov NCT02315066). Up to four patients will be enrolled at the dose level of 0.3mg/kg of PF-04518600. This arm will be closed at this time to further enrollment due to lack of clinical efficacy and competing options of higher priority at our institution.

Lead-in safety evaluation for Arm B-F

A lead-in safety evaluation for Arm B-F will be conducted to confirm the safety and tolerability of the treatment combination. Up to 30 patients in arm B, 24 patients in arms C-D and up to 21 patients in arms E-F will be enrolled. Enrollment must be halted while the first 6 patients in each treatment arm are evaluated for safety (i.e. after all patients have received 2 cycles of therapy, or been followed for at least 56 days from the start of treatment).

The treatment combination will be considered as safe and continue to enroll a total of 30 patients (arm B) or 24 patients (arms C-D) or 15 patients (arms E-F) when there are no more than 1 out of 6 patients with DLTs in the first cycle (28 days) of treatment. If any patients in the first 6 of each treatment arm withdraw from the study without a DLT event prior to completing the first cycle of treatment, they will be replaced for the assessment of DLT rate. This will allow for early identification of significant toxicities and early stoppage in potentially toxic arms. If 2 or more out of 6 patients with DLTs in the first cycle of treatment, then additional 6 patients will enroll at a lower dose level. If no more than 1 out of the additional 6 patients treated with lower dose level experienced DLTs, this treatment combination will be considered as safe and continue to enroll to a total of 30 patients (arm B), 24 (arms C-D) or 15 patients (arms E-F). If 2 or more out of these 6 additional patients experienced DLTs, then this arm will be halted.

Arm F will be closed at this time to further enrollment due to lack of clinical efficacy and competing options of higher priority at our institution.

Futility Monitoring for Arms B-F

The primary endpoint of Arm B-F is the achievement of composite complete response (CRc) within 3 months of therapy initiation in patients with RR AML. The method of Thall, Simon and Estey (1995) will be used to monitor efficacy and safety. After the lead-in, shiny applications were used to generate the operating characteristics for toxicity and futility monitoring, respectively (http://qcprlshinypro.mdanderson.edu/postprobtoxicity/; http://qcprlshinypro.mdanderson.edu/postprobfutility/).

The historical data suggested a composite complete response (CRc) rate of 30% in patients with R/R AML with a variety of different therapies[4,110,119-122], and a target response rate is 45%. The study arm will be stopped early if the data suggest that:

$$Pr(P_E > P_H + 0.15 \mid data) < 0.05,$$

where P_E and P_H are the CRc rates for experimental and historical treatment, respectively. That is, if at any time during the study we determine that there is less than 5% chance that the CRc rate improves over historical rate by more than 15%, the arm will be stopped due to futility. PE is assumed to follow a prior of Beta (0.6, 1.4). The futility monitoring will be conducted starting from the 10th patient in cohort size of 5 patients except the last cohorts with less than 5 patients. The design parameters are set the same for arms B-F, while separate futility monitoring analyses were conducted to accommodate different numbers of patients among these arms.

Arm F will be closed at this time to further enrollment due to lack of clinical efficacy and competing options of higher priority at our institution.

Arm B

The stopping boundaries for efficacy based on these assumptions and monitoring conditions are provided in Table 14. The operating characteristics are summarized in Table 15.

If the study arm is not stopped early and 24 patients have been treated and evaluated in the study arm, assuming 8 of the 24 patients achieve CRc under the combination treatment, then the 95% credible interval for CRc rate will be (0.17, 0.52).

Table 14. Stopping boundaries for futility monitoring in Arm B

# of patients evaluated for response	Stop the arm if # of patients with response is less than or equal to:
10	0-2
15	0-3
20	0-5
24	Always stop with this many patients

Table 15. Operating characteristics for futility monitoring in Arm B-D

True response rate	Prob(stop the arm early)	Average sample size
0.15	0.952	11.7
0.25	0.702	15.6
0.30	0.525	17.8
0.35	0.357	19.8
0.45	0.126	22.5
0.55	0.031	23.6
0.65	0.005	23.9

Arm C-D

The stopping boundaries for efficacy based on these assumptions and monitoring conditions are provided in Table 16. The operating characteristics are summarized in Table 17.

If the study arm is not stopped early and 18 patients have been treated and evaluated in the study arm, assuming 6 of the 18 patients achieve CRc under the combination treatment, then the 95% credible interval for CRc rate will be (0.15, 0.54).

Table 16. Stopping boundaries for futility monitoring in Arm C-D

# of patients evaluated for response	Stop the arm if # of patients with response is less than or equal to:
10	0-2
15	0-3
18	Always stop with this many patients

Table 17. Operating characteristics for futility monitoring in Arm C-D

True response rate	Prob(stop the arm early)	Average sample size
0.15	0.878	11.3
0.25	0.585	13.6
0.30	0.428	14.8
0.35	0.291	15.8
0.45	0.108	17.2
0.55	0.029	17.8
0.65	0.005	18.0

Arm E-F

The stopping boundaries for efficacy based on the same assumptions and monitoring conditions are provided in Table 18. The operating characteristics are summarized in Table 19. If the study arm is not stopped early and 15 patients have been treated and evaluated in the study arm, assuming 5 of the 15 patients achieve CRc under the combination treatment, then the 95% credible interval for CRc rate will be (0.13, 0.56).

Arm F will be closed at this time to further enrollment due to lack of clinical efficacy and competing options of higher priority at our institution.

Table 18. Stopping boundaries for futility monitoring in Arm E-F

# of patients evaluated for response	Stop the arm if # of patients with response is less than or equal to:
10	0-2
15	Always stop with this many patients

Table 19. Operating characteristics for futility monitoring in Arm E-F

True response rate	Prob(stop the arm early)	Average sample size
0.15	0.820	10.9
0.25	0.526	12.4
0.30	0.383	13.1
0.35	0.262	13.7
0.45	0.100	14.5
0.55	0.027	14.9
0.65	0.005	15.0

Toxicity Monitoring for Arm B-F

The method of Thall, Simon and Estey will be used for toxicity monitoring for this study. Denote the probability of DLT by P_T. We assume as a priori, P_T ~ beta (0.3, 1.7). Our stopping rule is: if 2 or more out of 6 patients with DLTs in the first cycle of treatment, then additional 6 patients will enroll at a lower dose level. If 2 or more out of these 6 additional patients experienced DLTs, then this arm will be halted. Otherwise, we will stop the arm if $Pr(P_T > 0.15 \mid data)>0.80$. That is, we will stop the arm for new patient enrollment if at any time during the study, we determine that there is more than 80%

chance that the toxicity rate is more than 15%. Again, the design parameters are set the same for arms B-F, while separate toxicity monitoring analyses were conducted to accommodate different numbers of patients among these arms.

Arm F will be closed at this time to further enrollment due to lack of clinical efficacy and competing options of higher priority at our institution.

Arm B

The toxicity stopping rule will be applied starting from the 6th patient, and then in cohort size of 3. Stopping boundaries corresponding to the above stopping rule are listed in Table 18. The operating characteristics are summarized in Table 19.

Table 18. Early stopping boundaries for toxicity monitoring arm B

# of patients (in cohort size of 3, starting from the 6th patient)	Stop the arm if there are this many patients with toxicities:
6	2-6
9	3-9
12	4-12
15	4-15
18	5-18
21	5-21
24	Always stop

Table 19. Operating characteristics for toxicity monitoring arm B

True toxicity rate	Prob(stop the arm early)	Average sample size
0.10	0.163	21.4
0.15	0.342	19.0
0.20	0.555	16.0
0.25	0.731	13.4
0.30	0.856	11.0
0.40	0.976	8.0

Arm C-D

The toxicity stopping rule will be applied starting from the 6th patient, and then in cohort size of 3. Stopping boundaries corresponding to the above stopping rule are listed in Table 18. The operating characteristics are summarized in Table 19.

Table 20. Early stopping boundaries for toxicity monitoring arm C-D

# of patients (in cohort size of 3, starting from the 6th patient)	Stop the arm if there are this many patients with toxicities:
6	2-6
9	3-9
12	4-12

15	4-15
18	Always stop

Table 21. Operating characteristics for toxicity monitoring arm C-D

True toxicity rate	Prob(stop the arm early)	Average sample size
0.10	0.137	16.5
0.15	0.290	15.0
0.20	0.485	13.1
0.25	0.653	11.4
0.30	0.771	10.1
0.40	0.936	7.8

Arm E - F

The toxicity stopping rule will be applied starting from the 6th patient, and then in cohort size of 3. Stopping boundaries corresponding to the above stopping rule are listed in Table 22. The operating characteristics are summarized in Table 23.

Arm F will be closed at this time to further enrollment due to lack of clinical efficacy and competing options of higher priority at our institution.

Table 22. Early stopping boundaries for toxicity monitoring arm E-F

# of patients (in cohort size of 3, starting from the 6^{th} patient)	Stop the arm if there are this many patients with toxicities:
6	2-6
9	3-9
12	4-12
15	Always stop

Table 23. Operating characteristics for toxicity monitoring arm E-F

True toxicity rate	Prob(stop the arm early)	Average sample size
0.10	0.122	13.9
0.15	0.264	12.8
0.20	0.410	11.6
0.25	0.562	10.3
0.30	0.685	9.3
0.40	0.874	7.6

Statistical Analysis Plan

Demographic/clinical characteristics and safety data will be summarized using descriptive statistics such as mean, standard deviation, median and range. The composite complete response (CRc) rates, partial response (PR), hematologic improvement (HI) rate, 4-week and 8-week mortality will be estimated along with the

95% credible intervals. Kaplan-Meier method will be used to estimate the relapse-free survival (RFS), morphologic leukemia free survival (MLFS), time to next therapy (TNT) and overall survival (OS). The two-sided log-rank tests will be used to assess the differences of time to events between groups. Cox proportional hazards regression model will be used to determine associations between MRD and OS.

All patients who received at least one dose of study drug will be included in the intent-to-treat analysis for efficacy and safety. We will follow standard reporting guidelines for adverse events. Safety data will be summarized by category, severity and frequency. Paired t-tests will be used to determine the immunological and molecular changes in the peripheral blood and bone marrow from baseline to the predefined time-points on-therapy.

12.0 PROTOCOL ADMINISTRATION

This study will be monitored by the MD Anderson IND Office and a protocol-specific monitoring plan will be followed.

Protocol amendments

Changes to the protocol will be made only when protocol amendments have been signed by the principal investigator and approved by Pfizer and the IRB of the study center.

Archival of data

MD Anderson-IND study must retain all records *indefinitely*.

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