Targeting polo-like kinase 1 in acute myeloid leukemia

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Abstract: Polo-like kinase 1 (Plk1) plays a number of important roles in the passage of cells through mitosis. It is expressed at high levels in a variety of malignancies, including acute myeloid leukemia (AML). Inhibition of Plk1 results in cell cycle arrest and apoptosis, and has anti-tumor effects in pre-clinical models. A number of Plk1 inhibitors have been developed, some of which have entered clinical trials. Of these, volasertib (BI6727) has been most extensively studied clinically in AML. Volasertib has demonstrated antileukemic activity in AML, both as a single agent and when combined with low-dose cytarabine. It is well tolerated, with the major toxicity being reversible myelosuppression. A recently completed phase III clinical trial in older AML patients will address the question of whether adding this agent to low-dose cytarabine is associated with a survival advantage.

Keywords: acute myeloid leukemia, chemotherapy, leukemia, polo-like kinases, volasertib

Acute myeloid leukemia

Acute myeloid leukemia (AML) is an aggressive hematologic malignancy characterized by a clonal maturation arrest at an early myeloid progenitor stage, and the proliferation of primitive myeloblasts. This results in the accumulation of blast cells in the bone marrow leading to severe cytopenias and associated complications. The median age of AML is approximately 70 and the frequency increases dramatically above age 60 (SEER, 2014).

The treatment of younger and more fit older patients consists of intensive induction chemotherapy, using cytarabine plus an anthracycline, to achieve a complete remission (CR), followed by several cycles of consolidation chemotherapy. CR rates are in the 70% range in patients under age 60, and 50–55% in those over age 60 [Tallman *et al.* 2005; Grimwade *et al.* 2010; Mrozek *et al.* 2012]. However, the majority of patients will subsequently relapse. Cytogenetics and molecular mutations are important predictors of both CR and relapse with chemotherapy. Adverse risk cytogenetic groups include monosomal and complex karyotypes, as well as 3p26, 17p and 11q23 abnormalities. CR rates with induction chemotherapy in these patients are in the 30–50%

range, with 5-year overall survival (OS) of 10% or less [Grimwade *et al.* 2001, 2010; Gupta *et al.* 2005; Farag *et al.* 2006]. Among molecular mutations, *fms*-like tyrosine kinase internal tandem duplications (FLT3-ITD) are associated with a higher relapse rate and inferior survival [Mrozek *et al.* 2012; Linch *et al.* 2014], while nucleophosmin (NPM1) mutations are associated with a superior CR rate and OS [Schnittger *et al.* 2005; Mrozek *et al.* 2012]. Allogeneic hematopoietic stem-cell transplantation (HSCT) in CR can reduce the probability of relapse in poor risk patients, but many patients are not candidates for transplant owing to advanced age and comorbidities. Furthermore, the inability to achieve CR may preclude transplant, and success rates with HSCT are lower in poor risk patients [van Gelder *et al.* 2013]. In older patients, the 5-year OS with intensive chemotherapy is in the 10% range; for older patients with adverse risk karyotypes, there is little survival benefit with such aggressive treatment approaches, due to the low CR rates and brief CR duration [Gupta *et al.* 2005; Farag *et al.* 2006; Kantarjian *et al.* 2006; Grimwade *et al.* 2010]. For patients with relapsed/refractory AML, results are dismal and have only marginally improved in recent years [Pemmaraju *et al.* 2015].

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In older patients who are not considered suitable for intensive therapy based on comorbidities and performance status, therapeutic options are limited. Management with supportive care alone, with hydroxyurea to control peripheral blast counts, is associated with a median OS of 3–4 months and 1-year OS less than 20% [Harousseau *et al.* 2009]. Low-dose cytarabine is widely used in such older patients. The MRC-15 trial demonstrated a CR rate of approximately 20% in such older patients, with an associated survival benefit compared with supportive care plus hydroxyurea [Burnett *et al.* 2007]. However, this benefit was restricted to patients with standard or favorable risk cytogenetics; those with adverse risk cytogenetics had no CRs and no survival benefit. Furthermore, even in more favorable risk groups CRs were always transient. Hypomethylating agents, including azacitidine and decitabine, have demonstrated activity in older patients with AML, and produce superior OS compared with best supportive care [Fenaux *et al.* 2010; Kantarjian *et al.* 2012; Dombret *et al.* 2014]. Response rates and OS with hypomethylating agents are at least comparable to those of low-dose cytarabine [Dombret *et al.* 2014]. However, these agents are not curative, and virtually all patients will eventually experience disease progression. Although many novel agents have been studied or are currently in clinical trials in older patients with AML, no agent has been demonstrated to produce a survival benefit to date compared with standard treatments. There is therefore an urgent need to develop and test novel therapies in such patients.

Polo-like kinases

Polo-like kinases (Plks) constitute a family of serine/threonine kinases which regulate several key steps in the passage of cells through mitosis. In mammals, four members of the Plk family have been identified, each of which contains both a serine/threonine kinase domain and a polo-box domain [Winkles and Alberta, 2005; Strebhardt, 2010]. Plk1 is the most extensively characterized of these. It is expressed primarily during the G2 and M phases of the cell cycle where it plays multiple crucial roles, including mitotic spindle assembly, transition from metaphase to anaphase, chromatid separation and the onset of cytokinesis [Dai *et al.* 2002; Hansen *et al.* 2004; van Vugt *et al.* 2004; Strebhardt, 2010]. Plk1 also plays a key role in regulating checkpoint controls, including activation of the cyclin-dependent kinase Cyclin B/Cdk1 which controls entry into mitosis

[Chopra *et al.* 2010]. In addition, Plk1 phosphorylates the antiapoptotic protein Bcl-xl [Tamura *et al.* 2009]; inhibition of Plk1 decreases p-Bcl-xl expression, which may thereby promote apoptosis [Ikezoe *et al.* 2009].

Plk1 is expressed at very low levels in most normal tissues, including kidney, liver, brain, lung and pancreas [Winkles *et al.* 2005]. In contrast Plk1 is expressed at higher levels in tissues with rapidly proliferating cell populations, including placenta, spleen, ovary and testis [Winkles and Alberta, 2005]. Plk1 is overexpressed in a wide variety of cancers, including non-small cell lung [Wolf *et al.* 1997], breast [Wolf *et al.* 2000], ovarian [Weichert *et al.* 2004] and head and neck squamous carcinomas [Knecht *et al.* 2000], as well as melanoma [Strebhardt *et al.* 2000] and diffuse large B cell lymphoma [Liu *et al.* 2007]. Overexpression of Plk1 has been correlated with an inferior prognosis in several of these malignancies [Wolf *et al.* 1997; Knecht *et al.* 2000; Weichert *et al.* 2004].

Inhibition of Plk1 in tumor cell lines, using small interfering RNA or small molecule inhibitors, results in inhibition of cell proliferation with cell cycle arrest at the G2/M phase. This is associated with disorganized spindle appearance and an increase in histone H3 levels followed by apoptotic cell death [Liu and Erikson, 2003; Lenart *et al.* 2007]. Such inhibition has also been shown to reduce tumor growth in mouse xenograft models [Stegmaier *et al.* 2007; Renner *et al.* 2009]. Plk1 inhibition does not appear to be dependent on functional p53; in fact, there is evidence that Plk-1 mediated cytotoxicity is increased in cells with nonfunctional p53 [Craig *et al.* 2014].

Plk1 mRNA and protein have also been found to be overexpressed in multiple AML cell lines, as well as in blast cells from the majority of patients with AML [Ikezoe *et al.* 2009; Renner *et al.* 2009]. In contrast, Plk1 expression in bone marrow and peripheral blood mononuclear cells, and in normal CD34-positive progenitor cells, is low [Ikezoe *et al.* 2009]. Expression in AML cells did not appear to correlate with cytogenetic subgroups in one study [Renner *et al.* 2009]. Inhibition of Plk1 by small interfering RNA or a selective Plk1 small molecule inhibitor *in vitro* is associated with a marked inhibition in proliferation of AML cell lines, accompanied by an accumulation of cells in the G2/M phase and induction of apoptosis. Incubation of fresh AML cells with a Plk1 inhibitor is also associated with a marked reduction in clonogenic growth.

In contrast, normal CD34-positive progenitor cells, and bone marrow mononuclear cells, were largely insensitive to inhibition [Ikezoe *et al.* 2009; Renner *et al.* 2009].

In severe combined immunodeficiency mouse xenograft models, Plk1 inhibition resulted in a marked reduction in tumor volumes using the AML cell line HL-60 [Valsasina *et al.* 2012]. In the same study, using a murine model of disseminated leukemia using patient-derived AML cells, PLK1 inhibition was also associated with a prolongation in survival, and showed evidence of synergy when combined with cytarabine, with further prolongation in survival.

Development of PLK1 inhibitors

A number of different small molecule inhibitors of Plk1 are in preclinical and clinical development (see Table 1). GSK4611364A (GlaxoSmithKline, London, UK) is a highly selective thiophene amide inhibitor of Plk1 which induces mitotic arrest and inhibition of tumor growth in xenograft models. A phase I study has been completed in patients with solid tumors [Olmos *et al.* 2011].

Several newer Plk1 inhibitors have reported activity in preclinical studies. TAK-960 is a potent orally bioavailable selective Plk1 inhibitor which was shown to have activity against a variety of tumor cell lines, including K562 leukemia cells *in vitro*. This agent also produced marked growth inhibition of AML MV4-11 cells in a mouse xenograft model [Hikichi *et al.* 2012]. A phase I study has been completed in patients with advanced solid tumors, but has not yet been published. NMS-P937, another orally bioavailable agent, has been shown to have a high degree of activity and selectivity for Plk1 with a half maximal inhibitory concentration (IC₅₀) of 0.002 $\mu\text{mol/L}$ [Valsasina *et al.* 2012]. It has produced marked inhibition of growth in both leukemia and colon carcinoma cell lines, and inhibition of acute monoblastic leukemia in a mouse model [Casolaro *et al.* 2013]. This agent has not yet been studied in humans.

BI2536 (Boehringer-Ingelheim, Ingelheim, Germany) is a highly potent Plk1 inhibitor that induces cell cycle arrest and apoptosis [Lenart *et al.* 2007; Steegmaier *et al.* 2007]. A phase I study with this agent has been reported in patients with solid tumors [Hofheinz *et al.* 2010]. When administered on a day 1 and 8 dosing schedule in this study, the maximum

tolerated dose (MTD) was 100 mg; the dose-limiting toxicity was grade 3–4 myelosuppression. In addition, a phase I/II trial of this agent was reported in older patients with relapsed/refractory AML [Müller-Tidow *et al.* 2013]. The MTD was 200 mg when given in a similar day 1 and 8 dosing schedule, and 350 mg in a day 1 schedule, with the major grade 3–4 toxicities being myelosuppression with associated neutropenic sepsis. Of 54 evaluable patients, two achieved CR and three a partial response, for an overall response rate of 9%. Evidence of cell cycle arrest was seen in AML blasts *in vivo*. Further development of this agent was subsequently discontinued in favor of BI6727 due to the latter's improved pharmacokinetic profile (see below).

Rigosertib

ON01910 (Onconova Therapeutics, Newtown, PA), also known as rigosertib, is a non-adenosine triphosphate (ATP) competitive benzyl styryl sulfone analog that inhibits Plk1 as well as PI3Kinase; and has broad activity against a variety of tumor cell lines [Gumireddy *et al.* 2005]. As with other Plk1 inhibitors, it induces mitotic arrest and apoptosis. Two phase I studies with this agent have recently been completed in patients with advanced solid tumors [Advani *et al.* 2014; Bowles *et al.* 2014]. A recent paper reported on the use of rigosertib, given as a 72 h continuous intravenous infusion in patients with myelodysplastic syndromes (MDS), most with high-risk International Prognostic Scoring System (IPSS) scores, who had previously been treated with hypomethylating agents (HMAs) [Silverman *et al.* 2014]. Of 40 patients, 12 (40%) achieved a partial or complete marrow blast response, while several others experienced hematologic improvement associated with stable marrow blasts. The drug was well tolerated, with modest myelotoxicity; other toxicities included fatigue, nausea, diarrhea and hematuria (mainly grade 1–2). A phase I study has also been reported using oral rigosertib in high-risk MDS [Komrokji *et al.* 2013]; notable nonhematologic toxicities included urothelial inflammation, manifest as dysuria and hematuria. As with the previous study, some hematologic responses were observed.

A phase III randomized trial has subsequently been reported with this agent in patients with high-risk MDS who had failed to respond to, relapsed or progressed after, receiving treatment with HMA [Garcia-Manero *et al.* 2014]. Patients

Table 1. Summary of Polo-like kinase 1 inhibitors and status of development.

Agent	Company	Regimen	Disease	Phase	Reference
GSK4611364A	GlaxoSmithKline	single agent	Solid tumours	I	Olmos
TAK-960	Millennium	single agent	Solid tumours	I	(pending)
NMS-P937	Nerviano	single agent			(preclinical)
Rigosertib	Onconova	single agent	Solid tumours	I	Bowles, Advani
		single agent	MDS/AML	I/II	Silverman, Komrokji
		single agent	MDS	III	Garcia-Manero
		single agent	AML/ALL/MPD	I/II	(pending)
BI2536	Boehringer-Ingelheim	single agent	AML	I/II	Müller-Tidow
Volasertib	Boehringer-Ingelheim	single agent	Solid tumours	I	Schöffski
		single agent	AML	I/II	Dohner, Bug
		+ LDAC	AML	I/II	Dohner
		+ LDAC	AML	III	(pending)

ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; LDAC, low-dose cytarabine; MDS, myelodysplastic syndrome; MPD, myeloproliferative disease.

were randomized between rigosertib, given as 72 h continuous intravenous infusion *versus* best supportive care. Although this study did not demonstrate a significant difference in OS between the two arms, an improvement in OS in favor of the rigosertib arm was observed within certain subgroups, including those with primary HMA failure (8.6 *versus* 5.3 months, $p = 0.04$) and very high-risk revised-IPSS scores.

Several of the early phase studies with rigosertib have included patients with AML, either exclusively or combined with patients with MDS. These have only been reported in abstract form to date, but it has been noted that patients with AML with higher blast percentages were less likely to respond [Navada *et al.* 2013]. A phase I/II study in AML, ALL and myeloproliferative disorders has just been completed [ClinicalTrials.gov identifier: NCT01167166], and the results are pending.

Volasertib

BI6727 (Boehringer-Ingelheim), now called volasertib, is a second in-class dihydropteridine derivative. It is a potent ATP-competitive selective inhibitor of Plk1, and also inhibits Plk2 and Plk3 (IC₅₀ 0.87, 5 and 56 nM/L, respectively). This inhibition is highly selective, as it did not show inhibitory activity against over 50 other kinases at clinically relevant concentrations

[Rudolph *et al.* 2009]. Volasertib has shown activity *in vitro* against a wide variety of tumor cell lines, including colon, melanoma, lung, lymphoma and AML lines [Rudolph *et al.* 2009]. Cellular effects are similar to those of other Plk1 inhibitors, with arrest in G2/early M phase and subsequent induction of apoptosis. It also demonstrates broad antitumor activity *in vivo* in multiple mouse xenograft models.

As with its predecessor compound, the major dose-limiting toxicity in phase I studies in solid tumors has been grade 3–4 reversible myelosuppression [Schöffski *et al.* 2012]. In addition, transient QTc prolongation is typically seen, but no clinical sequelae of this have been reported to date. Mucositis is infrequent, and no neurotoxicity, cardiotoxicity or nephrotoxicity has been reported. Volasertib is both a substrate and inhibitor of P-glycoprotein (P-gp); therefore, drug–drug interactions with other P-gp substrates are expected but have not yet been described. When administered as a 1 h intravenous infusion the half life is approximately 110–115 h [Bug *et al.* 2011; Schöffski *et al.* 2012].

A phase I study was completed in patients with relapsed/refractory AML [Bug *et al.* 2011; Döhner *et al.* 2014a]. When dose escalated as monotherapy in a day 1 and 15 schedule, repeated every 4 weeks, the MTD was determined to be 450 mg [Döhner *et al.* 2014a]. The dose-limiting toxicity

at doses of at least 500 mg consisted primarily of mucosal inflammation, with esophagitis and gastrointestinal hemorrhage seen as well. At doses of at least 350 mg antileukemic activity was noted, with 5 of 43 (12%) CRs with incomplete count recovery (CRi) in this heavily pretreated population.

When combined with low-dose cytarabine (LDAC) 20 mg subcutaneously twice daily for 10 days, the MTD of volasertib was 350 mg intravenously given on a day 1 + 15 schedule, repeated every 4 weeks [Bug *et al.* 2011]. The major dose-limiting toxicity using this combination was myelosuppression; the CR (CR + CRi) rate in this study was 22%. There was no evidence of drug interactions between volasertib and LDAC.

A subsequent open-label randomized phase II study has been published comparing the combination of volasertib 350 mg intravenously on days 1 and 15 plus LDAC 20 mg subcutaneously twice daily for 10 days on a 28-day cycle, with LDAC alone in the same dosing schedule [Döhner *et al.* 2014b]. Patients could continue therapy until disease progression. This study enrolled 87 older patients with previously untreated AML who were not candidates for intensive chemotherapy based on physician judgment. The CR (CR + CRi) rate for the combination arm was 31% compared with 13% in the LDAC monotherapy arm. Notably, in patients with adverse risk cytogenetics the CR rate was 36% (5/14) in the combination arm *versus* 7% (1/14) in the LDAC monotherapy arm. There was a significantly longer event-free survival ($p = 0.021$) and OS ($p = 0.047$) in the volasertib + LDAC arm. There were more grade 3 adverse events in the combination arm, with respect to febrile neutropenia, documented infections and gastrointestinal events (mainly grade 3 diarrhea), but there was no difference in the 30- and 60-day mortality.

Based on these results, a larger (>600 patient) multicenter phase III double-blind randomized placebo-controlled trial was initiated with LDAC $\pm$ volasertib, using the same comparator groups and dosing schedule as in the phase II study [ClinicalTrials.gov identifier: NCT01721876]. Eligible patients included those aged 65 years and over with previously untreated AML who were not considered candidates for intensive chemotherapy, with a 2:1 randomization between study drug and placebo. Accrual to this study has now

been completed (as of November 2014), and results are pending.

Summary and future directions

Plk inhibitors represent a promising new class of anticancer agents. Volasertib is the first agent of its class to be studied clinically, and the first to proceed to phase III testing, in AML. Single-agent activity has been demonstrated in AML, and the combination with low-dose cytarabine is associated with increased antileukemic activity compared with cytarabine alone, with an acceptable toxicity profile. The current phase III study will determine whether OS is improved using this combination.

Given its limited nonhematologic toxicity, volasertib is also an attractive agent to consider in other combination regimens. A phase I study is planned combining this agent with induction chemotherapy in AML. Further preclinical studies are also warranted, evaluating potential synergy with other agents. Synergy with vincristine has been seen in leukemia cell lines [Ikezoe *et al.* 2009]. Exploratory studies combining these drugs with hypomethylating agents would also be worth considering in view of the activity and tolerability of both agents and their nonoverlapping mechanisms of action. Plk1 inhibitors may also have a potential role as maintenance therapy, particularly in older patients with AML who are not transplant candidates.

Other Plk1 inhibitors also warrant testing in AML. As mentioned, rigosertib has demonstrated activity in high-risk MDS. It may offer an advantage of limited myelotoxicity at the doses used, but its use may be limited by nonhematologic bladder toxicity. The continuous infusion schedule may offer additional theoretical advantages, by hitting a higher proportion of leukemic cells as they enter mitosis; its dual mechanism of action may produce additional antileukemic activity. Although it appears to have limited activity in AML as a single agent, it may have greater activity in combination. Some of the newer agents such as NMS-P937 have higher selectivity for Plk1 and a lower IC₅₀, which may result in different efficacy and toxicity profiles. The oral Plk1 inhibitors, including TAK960 and NMS-P937, would offer a potential advantage of convenience, particularly in the maintenance setting, in older patients.

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