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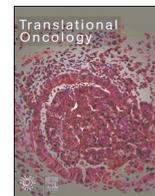
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The AGILE trial of ivosidenib plus azacitidine versus azacitidine alone: How many limitations is too many?

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ABSTRACT

The AGILE trial compared ivosidenib and azacitidine versus azacitidine for IDH1-mutant acute myeloid leukemia (AML) in elderly patients who were ineligible to receive intensive chemotherapy. While the results of this trial appear encouraging, various concerns become evident from the study design and methodology. First, the AGILE trial did not use post-protocol therapy that met the current standard of care. Second, researchers continued patient enrollment despite knowledge of the survival benefit of azacitidine plus venetoclax shown in the VIALE-A trial, resulting in an inferior control arm. Third, the primary endpoint of AGILE was changed from overall survival (OS) to event-free survival (EFS), and the sample size was reduced to expedite the results. Finally, the trial was halted early based on a non-primary endpoint, which likely led to exaggerated effect size or misleading results. We discuss these limitations and continue to advocate for careful analysis of study design to ensure that appropriate and accurate outcomes are implemented in future studies.

The AGILE trial (NCT03173248) compared ivosidenib and azacitidine against placebo and azacitidine among elderly patients diagnosed with isocitrate dehydrogenase 1 (IDH1) mutant acute myeloid leukemia (AML) who are ineligible to receive intensive chemotherapy [1]. AGILE exemplifies the challenges of conducting a clinical trial in a therapeutic environment that is both shifting and expanding. Expanding treatment options for patients with AML is focusing on innovative targeted therapies in the hopes of revolutionizing mono and combination therapy [2]. While AGILE's findings appear encouraging, we have four major concerns with the AGILE trial and its timeline.

Before addressing flaws in trial design, it is important to understand the chronology of events surrounding AGILE. As shown in the Fig. 1, researchers began enrolling patients in March 2018. The original statistical plan called for accrual of 392 patients with overall survival (OS) as the primary endpoint [1]. At this time, azacitidine was the standard of care. On July 20th, 2018, approximately four months into the study, the US Food & Drug Administration (FDA) approved ivosidenib for the treatment of IDH1-mutated AML, and it rapidly became used among leukemia providers as second-line, third-line or salvage therapy [3]. On March 23rd, 2020, Genentech announced the results of the VIALE-A study [3]. With a sample size of 431 and a primary endpoint of OS, VIALE-A demonstrated that azacitidine and venetoclax (Aza-Ven)

produced an OS benefit when compared to azacitidine alone (median OS of 14.7 months for Aza-Ven vs. 9.6 months for azacitidine + placebo), changing the standard of care to Aza-Ven [4,5].

AGILE continued to enroll patients over the ensuing year. On May 26th, 2020, two months after the VIALE-A results, AGILE investigators modified their primary endpoint from OS to event-free survival (EFS) [1]. This would lower the necessary sample size to demonstrate a significant result.

AGILE was then halted in the following year on May 27th, 2021 by the Data and Safety Monitoring Board (DSMB) due to an imbalance of deaths between the trial arms. When it closed, AGILE had a sample size of 146 patients, rather than the initial projection of 392 patients [1]. Overall, AGILE demonstrates four concerns.

Limited post-protocol therapy

Post-protocol therapy refers to treatments administered after the therapies of a clinical trial have been completed or when a patient's disease state progresses. Post-protocol therapy influences all endpoints that occur after the initial EFS or progression free survival (PFS) event, including overall survival. Inappropriate post-protocol care may result from imbalance across study arms, or, in the case of the AGILE trial, if

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both arms receive post-protocol therapy that falls short of the current standard of care [6]. Just four months into the study, ivosidenib was FDA approved for use in IDH1-mutant AML and rapidly gained uptake among leukemia physicians, and yet, only two patients on the control arm of AGILE received post-protocol ivosidenib when their AML progressed [7]. There are three issues with this sequence of events.

First, the AGILE investigators reasoned that ivosidenib could not be considered for post-protocol therapy due to the drug's lack of approval by the European Medicines Agency (EMA) and the global design of the trial [8]. However, it is likely that Agios Pharmaceuticals,[†] both the industry-sponsor of AGILE and manufacturer of ivosidenib, could have paid for and provided ivosidenib as a salvage agent as part of trial protocol for the control arm. Lack of EMA approval does not prevent a company from providing its drug upon progression to control arm patients.

Second, accrual of patients from the United States (US) stopped in October 2018, likely due to trial results that led to the FDA approval of venetoclax in combination for patients with AML that November [9]. This rendered AGILE non-applicable to the US. Yet, the AGILE trial was used for US FDA approval of ivosidenib in combination with azacitidine for IDH-1 mutant AML [10]. This breaks a fundamental rule of regulatory drug approval: if a pharmaceutical company seeks US approval, it should aspire to inform care in the US. AGILE could not, as the US standard of care post-protocol was not followed.

Lastly, because of poor post-protocol therapy, AGILE is incapable of answering the relevant question: is it better to combine ivosidenib with front-line therapy, or can its use be reserved for salvage, possibly yielding equivalent (or superior if preceded by Aza-Ven) overall survival with less cost and toxicity?

Obsolete control arm

Patients on the control arm of AGILE continued to be randomized to azacitidine + placebo despite investigators knowing that Aza-Ven had an OS advantage since the spring of 2020, and the publication of VIALE-

A in August of that year [4]. AGILE cannot answer the question of whether ivosidenib and azacitidine is superior to the current standard of care: venetoclax and azacitidine. This is particularly salient as venetoclax and azacitidine appear to work particularly well in IDH-mutant AML, with a median OS of 17.5 months [1,6].

Changes to the primary endpoint and sample size

The primary endpoint of AGILE was changed from OS to EFS, and the sample size was decreased from 392 to a planned 200 patients [1]. Outcome switching is not always wrong or impermissible, but the reasons for it must be sound [7]. In this case, the authors contest that EFS better captures the value of a drug on protocol and is not confounded by post-protocol care. But this argument is illogical. First, AGILE had an extremely poor rate of post-protocol ivosidenib (only 2 patients), so it is not clear why this could be their concern. Second, this argument misunderstands the purpose of front-line studies. The purpose is to know if the routine upfront use of the ivosidenib + azacitidine is superior to what physicians are currently practicing. Since ivosidenib has already become a de facto second-line option, use of the drug post-protocol is a feature and not a bug. Appropriate post-protocol care never 'confounds' an overall survival analysis, it asks the relevant question. AGILE must show routine upfront use is superior to the current standard, being second-line use, and as such, endpoint switching is unjustified by the authors.

Halting trial early based on a non-primary endpoint

It's noteworthy that the trialists utilized the trial's former primary endpoint, OS, to halt the trial despite changing the endpoint to EFS. The trial was halted early due to an observed imbalance between the trial arms ($n = 74$; $n = 28$ ivosidenib + azacitidine, $n = 46$ azacitidine + placebo) [1]. This contradicts the trial's original protocol, which indicated that the first interim analysis would begin once 93 deaths were observed. The tension here is the following: before the trial embarked,

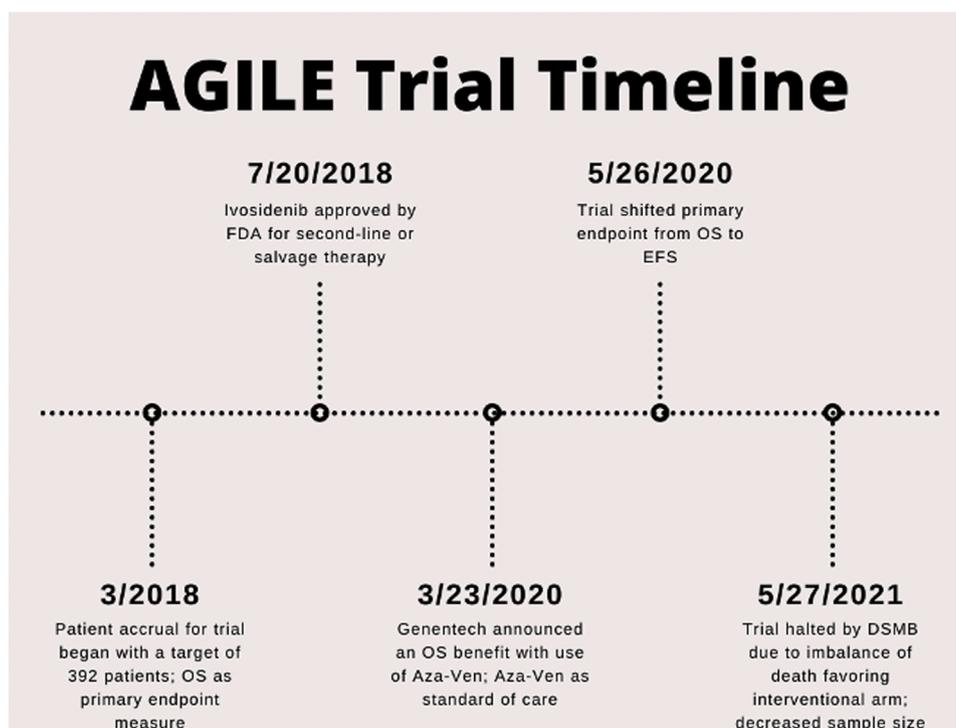


Fig. 1. Timeline of events pertinent to the AGILE trial.

Abbreviation: FDA, US Food and Drug Administration; OS, overall survival; EFS, event-free survival; Ven, venetoclax; Aza, azacitidine; DSMB, Data and Safety Monitoring Board; PFS, Progression-free survival.

researchers were comfortable with 93 deaths occurring before anyone would halt the study. Now, after 74 deaths, they claim it would be unethical to continue. This claim contradicts the initial plan of the trial. Of note, early halting has long been recognized as a bias that will distort the magnitude of benefit [8].

Conclusion

In conclusion, although performing any randomized trial is challenging, AGILE is incapable of answering the relevant question facing doctors and patients: whether ivosidenib + azacitidine followed by standard of care is superior to azacitidine + venetoclax followed by ivosidenib. Endpoint switching, early termination, limited control arms, and limited post-protocol care all conspire against the trial. Ultimately, clinical trials are tools to best determine how to treat patients, and all other purposes, including marketing authorization, are secondary. We urge greater scrutiny with future studies.

[†]Note: The oncology business of Agios Pharmaceuticals was acquired by Servier Pharmaceuticals in 2021.

Authorship contribution

VP conceptualized study design; AB and KP reviewed the literature; VP reviewed and confirmed abstracted data; AB wrote the first draft of the manuscript; and all authors reviewed and revised subsequent and finalized draft of the manuscript.

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Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests.

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