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# Targeting Mutated *Isocitric Dehydrogenase* 1 (mIDH 1) in Acute Myeloid Leukemia (AML): Story of Ivosidenib

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In 2008, mutations in *isocitric dehydrogenase* 1 & 2 (mIDH 1 & 2) was first detected in glioblastoma multiforme (GBM) from among many types of solid tumour. The next year i.e. in 2009 acute myelogenous leukemia (AML) showed the presence of such mutation. mIDH 2 blocker enasidenib came into the market for the first time for adult recurrent and relapsed AML in 2017. But mIDH 1 blocker ivosidenib (AG-120) is approved in 2019 in recurrent and relapsed AML. At the end of 2019, it was approved for untreated adult AML. When it was in the early phase trial it became eligible for a special expanded access program as it showed encouraging results. The drug molecule's progress through preclinical and regulatory path is interesting. It is worthwhile to investigate how it received market authorization while the phase III trial was not over. Trial of both GBM and AML started in March 2014. Circumstances behind ivosidenib being first approved in adult recurrent and relapsed AML rather than in glioma where the mutation was first found are also discussed.

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**Introduction**

Acute myeloid leukemia (AML) is a severe form of acute hematological malignancy, especially for elderly patients who account for over 85% of diagnoses. Standard induction therapy with intensive cytotoxic chemotherapy for AML had remained unchanged for over four decades. While overall survival rates for patients aged 65 to 74 years have improved modestly over the last four decades, they remain unacceptably low with one year and five-year survival rates are 30% and less than 10% respectively [1]. Hence, second-line therapy was an unmet need that could not be addressed for a long time. In a seminal study at Johns Hopkins Kimmel Cancer Centre recurrent mutations in the active site of isocitrate dehydrogenase 1 (IDH1) in 12% of patients were shown among more than twenty thousand genes in 22 primary and secondary human glioblastoma multiforme samples in 2008 [2]. In 2009, Madris et al [3] at Washington University, St. Louis showed the same mutation in the acute myeloid leukemia genome.

Mutations in IDH1 occurred in a large fraction of young patients and most patients with secondary GBMs and were associated with an increase in overall survival. But in AML with IDH mutation had worse survival. Mutations in the active site of IDH1 at position R132 were discovered later in 2009 during an integrated genomic analysis [4].

In 2009, an analogous mutation in the *IDH2* gene at position R172 was discovered in patients with gliomas including astrocytoma's and

oligodendrogliomas [5], mutations in both R172 and R140 are found in approximately 15-20% of patients with acute myeloid leukemia (AML) [6,7]. Cancer-associated metabolite 2-hydroxyglutarate accumulates in acute myeloid leukemia with isocitrate dehydrogenase 1 and 2 mutations [8]. As a result of this finding treatment in about 20% of this cancer with mutation in IDH 1 and 2 is revolutionized. This paradigm shift has made use of targeted therapy possible with revolutionary effect when used alone or in conjunction with less cytotoxic chemotherapy.

Mutations 1 and 2 in IDH (mIDH 1 & 2) lead to the production of an oncometabolite, 2-hydroxyglutarate (2HG), which exerts its pro-tumour effects, by regulating epigenetic enzymes. And they have now been targeted producing two drugs in quick succession in adult recurrent and relapsed AML, glioma, and in cholangiocarcinoma. They are first approved in adult recurrent and relapsed AML. mIDH 2 blocker enasidenib came first in 2017. mIDH 1 blocker ivosidenib is just approved in adult recurrent and relapsed AML. It did so well in the early phase trial and a special expanded access program that it is in the market while the phase 3 trial was not over.

**Ivosidenib (AG-120), Mutated Isocitric Dehydrogenase 1 (mIDH 1) inhibitor**

While susceptible IDH1 mutation could be detected by an FDA-approved test the targeted therapy for this mutation ivosidenib was finally approved by FDA on 20 July of 2018 in relapsed/refractory adult



AML. Approval was based on an open-label, single-arm, multicentre clinical trial (AG120-C-001, NCT02074839) that included 174 adult patients with relapsed or refractory AML. The median treatment duration was 4.1 months (range, 0.1 to 39.5 months). Twenty-one of the 174 patients (12%) received a stem cell transplant following ivosidenib treatment. FDA approved Abbott's Realtime IDH1 Assay for using ivosidenib in the second line in AML treatment for those who relapsed or were refractory to first-line therapy [9].

Ivosidenib is orally active. Its dose is 500 mg. It can be continued as long it responds and does not produce any serious adverse event where the physician decides against continuing therapy. It is also stopped in case transplantation is decided. The median treatment duration was 4.1 months (range, 0.1 to 39.5 months). Twenty-one of the 174 patients (12%) received a stem cell transplant following ivosidenib treatment. Efficacy was established based on the rate of complete remission (CR) plus complete remission with partial hematologic recovery (CRh), CR+CRh duration, and the rate of conversion from transfusion dependence to independence. The CR+CRh rate was 32.8% (95% CI: 25.8%-40.3%). This drug responds by approximately 2 months and remains effective 8.2 months on average (95% CI: 5.6 - 12 months). 110 patients who were treated with regular blood or platelet transfusion 37.3% that is 41 cases did not require transfusion anymore. Also, the other 38 patients (59.4%) of a total 64 became stable and did not deteriorate.

The most common adverse reactions ( $\geq 20\%$ ) were fatigue, differentiation syndrome, leukocytosis, arthralgia, diarrhea, dyspnea, edema, nausea, mucositis, electrocardiogram QT prolonged, rash, pyrexia, cough, and constipation. The recommended ivosidenib dose of 500 mg orally once a day is continued for at least 6 months so that response becomes evident.

### **Ivosidenib (AG-120) in glioblastomas**

In a genome-wide analysis, somatic mutations at codon 132 of the isocitrate dehydrogenase 1 gene (IDH1) was identified in approximately 12% of glioblastomas. Thus, more than 80% of secondary glioblastomas may show the mutation. Even a certain percentage of low-grade glioma with IDH1 mutation may progression to a glioblastoma [5]. Glioblastoma multiforme (GBM) is the most common and lethal type of brain cancer. Genetic alterations in GBMs could be detected [2] by sequencing 20,661 protein-coding genes. Both amplifications and deletions were detected by next-gen sequencing in 22 human tumor samples as described already. This led to the discovery of a variety of genes that were not known to be altered in GBMs namely recurrent mutations in the active site of isocitrate dehydrogenase 1 (IDH1) in 12% of GBM patients. Mutations in IDH1 were found mostly in young patients and many patients with secondary GBMs. An increase in overall survival was noticed in them establishing the value of unbiased genomic analyses in analyzing brain tumour and identifying potentially useful genetic alteration important for subtyping and finding targeted therapy of GBMs [8]. This might have posed some difficulty to infer from the trial of ivosidenib in GBM.

### **Ivosidenib (AG-120) in acute myelogenous leukemia (AML)**

IDH1/2 mutations are known to be heterozygous. They affect a single arginine residue of many types of solid tumors tested. Mutations in isocitrate dehydrogenase 1 and 2 (IDH1/2) were detected glioblastoma only. IDH1 mutations were identified later in 8% of acute myelogenous leukemia (AML) patients. An IDH1 mutation is gain-of-function in nature. Abnormal production and accumulation

of 2-hydroxyglutarate (2-HG) are noticed in cells with such mutation. 145 cases of AML marrow biopsies were subjected to genotyping. It identified 11 cases where IDH1 R132 mutation was present. Likewise, liquid chromatography-mass spectrometry was done as metabolite screening. It revealed increased 2-HG levels in IDH1 R132 mutant cells and sera. Astonishingly, two cases were detected where IDH2 R172K mutations were shown. IDH1/2 mutations were associated with normal karyotypes. Recombinant IDH1 R132C and IDH2 R172K proteins catalyze the novel nicotinamide adenine dinucleotide phosphate (NADPH)-dependent reduction of  $\alpha$ -ketoglutarate to 2-HG. It could be proved that IDH1 R132C mutation commonly found in AML reduces the affinity for isocitrate and increases the affinity for NADPH and  $\alpha$ -KG. Oxidative decarboxylation of isocitrate to  $\alpha$ -KG is prevented and instead conversion of  $\alpha$ -KG to 2-HG is precipitated. IDH1/2 mutations confer an enzymatic gain of function that dramatically increases 2-HG in AML. This explains the heterozygous acquisition of these mutations during tumorigenesis. 2-HG is an easily detected metabolic biomarker of mutant IDH1/2 enzyme activity [6]. Unlike GBM in AML patients, IDH1 mutations were associated with a lower complete remission rate (risk ratio 1.30, 95% CI: 1.04–1.63) [10]. Though later response rate and OS for both IDH-mutated and IDH wild-type AML patients were found almost the same but there was no improvement noted in mutation like in GBM [11].

## **Clinical Trial History**

### **Relapsed or refractory acute myeloid leukemia (AML)**

**Phase 1 trial:** Drug that inhibits the action of mutant isocitrate dehydrogenase 1 (IDH1) has successfully undergone preclinical study with benefit in in-vitro and animal models thus raising hope for treating patients with AML. Clinical early phase I trial showed positive results according to preliminary studies. Trial of orally administered AG-120 in subjects with advanced solid tumours, including glioma, with an IDH1 mutation, also started at about the same time (March 2014).

In this first human phase, I clinical trial of an IDH1-mutant inhibitor, 17 subjects with relapsed or refractory AML, and IDH1 mutations were recruited. Patients were put in one of four groups that received AG-120 (Agiros Pharmaceuticals; Cambridge, MA) in escalating doses. In the trial, NCT02073994 from March 2014 till the end of October 17, 4 patients out of 7 had complete remission. The findings were presented at the 26th Symposium on Molecular Targets and Cancer Therapeutics in Barcelona, Spain, sponsored by the European Organization for Research and Treatment of Cancer, the NCI, and the American Association for Cancer Research. AG-120 was given 100 mg twice daily, or 300 mg, 500 mg, or 800 mg once daily, for 28 days continuously per cycle. The maximum tolerated dose was not achieved, and one dose-limiting toxicity was found.

**Phase 3 trial:** Ivosidenib expanded access program in relapsed/refractory AML with an IDH1 mutation. But NCT03245424 is not a phase III trial. It was first submitted on August 7, 2017, and first posted on August 10, 2017. (Last Update Posted Date July 24, 2018). By this time on July 20, 2018 company got market authorization for sale worldwide in the above indication. Patients who were eligible for enrolment were entered into the study. A single strength dose of 500 mg by mouth once daily was decided on 28-day Cycles.

Depending on progression, toxicity, choice to continue, transplant, death, etc study would progress till marketing authorization. Safety assessments were performed at intervals per institutional standard of care for patients taking ivosidenib. These assessments as usual should



include but were not limited to pregnancy tests, ECG, clinical lab assessments, vital signs and physical exam findings, and assessment of adverse events of special interest (AESIs)/serious adverse events (SAEs). Toxicity severity was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03.

On May 2, 2019, the Food and Drug Administration approved ivosidenib (TIBSOVO, Agios Pharmaceuticals, Inc.) for newly-diagnosed acute myeloid leukemia (AML) with a susceptible IDH1 mutation, as detected by an FDA-approved test, in patients who are at least 75 years old or who have comorbidities that preclude the use of intensive induction chemotherapy. Approval was based on an open-label, single-arm, multicentre clinical trial (Study AG120-C-001, NCT02074839, 291 participants) of single-agent ivosidenib for newly diagnosed AML with an IDH1 mutation [12] detected by the Abbott Realtime TM IDH1 Assay.

Presently two phases III trials are recruiting (NCT03839771 & NCT03173248). However, none of them is for relapsed recurrent or refractory AML but newly diagnosed cases. The first study is of Ivosidenib or Enasidenib in combination with regular therapy on such patients having IDH1 or IDH2 Mutation (HOVON150AML). The sponsor is Stichting Hemato-Oncologie Voor Volwassenen Nederland and Collaborator is Deutsch-Österreichische Studiengruppe Akute Myeloische Leukämie (AMLSG). Another study is sponsored by the original Agios Pharmaceutical, Inc. This a phase 3, multicentre, double-blind, randomized, placebo-controlled study of Ivosidenib or Enasidenib in combination with induction therapy and consolidation therapy followed by maintenance therapy in patients with newly diagnosed acute myeloid leukemia or myelodysplastic syndrome with excess blasts-2, with an IDH1 or IDH2 mutation. These are big studies and will take a few more years to be completed.

## Glioblastoma

**Phase 1 trial:** On the other hand Agios Pharmaceuticals, Inc. started a phase 1, multicenter, open-label, dose-escalation and expansion, safety, pharmacokinetic, pharmacodynamic, and clinical activity study of orally administered AG-120 in subjects with advanced solid tumors, including glioma, with an IDH1 mutation (NCT02073994). The purpose of this Phase I, multicenter study was to evaluate the safety, pharmacokinetics, pharmacodynamics and clinical activity of AG-120 in advanced solid tumors, including glioma, cholangiocarcinoma, chondrosarcoma and other advanced solid tumors those harbor an IDH1 mutation. The first portion of the study was a dose escalation phase where cohorts of patients would receive ascending oral doses of AG-120 to determine maximum tolerated dose (MTD) and/or the recommended phase II dose. The second portion of the study is a dose expansion phase where four arms of patients will receive AG-120 to further evaluate the safety, tolerability, and clinical activity of the recommended Phase II dose. Anticipated time on study treatment is until disease progression, unacceptable toxicity occurs or at Investigator discretion. 170 participants would be the target. Study start date was March 2014. But estimated study completion date is June 2021. As of the data cut off, 35 patients (11 from escalation, 24 from expansion) with non-enhancing disease have been treated with single agent ivosidenib. Eighteen patients (51%) remained on treatment. Twenty-four patients had (WHO) classified Grade 2 tumors, eight had Grade 3 tumors, one had a Grade 4 tumor and two were unknown. Patients received daily doses of ivosidenib ranging from 300 mg to 900 mg. Twenty-eight patients received a daily dose of 500 mg, which

was selected as the expansion dose. The median age of these patients is 38 (ranging from 21-71). The median treatment duration was 16 months (ranging from 1.4 – 27.1 months). The median number of prior therapies was 2 (ranging from one to five). The median duration of last systemic therapy was 9.6 months.

Sixty-three percent of patients had previously received temozolomide and 57% percent had previously received radiotherapy. A safety analysis conducted for all 35 treated non-enhancing glioma patients as of the data cut-off demonstrated that ivosidenib was well-tolerated with a favourable safety profile in glioma patients. No dose limiting toxicities were observed. Most adverse events reported by investigators were mild to moderate, with the most common being headache, diarrhoea, nausea and vomiting. There were 5 patients with serious adverse events (SAE) and all were deemed unrelated to study treatment.

Efficacy data from all 35 non-enhancing glioma patients as of the data cut-off showed that two patients had a minor response by investigator assessment according to the Response Assessment in Neuro-Oncology for low grade glioma (RANO-LGG). Twenty-nine (83%) patients had stable disease. The median progression free survival (PFS) for all non-enhancing patients was 13 months, the median PFS for Grade 2 patients (n=24) has not been reached. For patients in the expansion arm (n=24), the average six-month tumor growth was 24% prior to treatment and 11% following treatment with ivosidenib.

This study (NCT02073994) also started in March 2014 but even an extensive recent review [13] could not throw any light as to why this trial was not given any boost and why ivosidenib is not yet approved by FDA for GBM. It appears that like early phase trials of many similar molecule such as DS-1001b, IDH305, and FT-2012, Enasidenib, and BAY-1436032 (ClinicalTrials.gov NCT03030066, NCT02381886, NCT03684811, NCT02273739, NCT02746081) ivosidenib in glioblastoma multiforme is “currently without early results”. Another such molecule is vorasidenib or AG-881 which need special mentioning as this molecule can cross blood brain barrier more easily.

## AG-881

AG-881, a brain-penetrant pan-IDH inhibitor along with ivosidenib in an orthotopic mouse xenograft model of human mIDH1-R132H glioma was studied. Preliminary data suggested that both molecules suppress the oncometabolite D-2-hydroxyglutarate (2-HG) in an orthotopic brain tumor model. At the doses explored, treatment with ivosidenib resulted in 85% maximal 2-HG inhibition, and treatment with AG-881 resulted in >98% inhibition of 2-HG levels. Neither molecule impeded the therapeutic effect of concomitant or sequenced radiation therapy. There are two trials, which are in the early phase and probably without result to date. A phase 1, multicenter, open-label, dose-escalation and expansion, safety, pharmacokinetic, pharmacodynamic, and clinical activity study of orally administered AG-881 in patients with advanced solid tumors, including gliomas, with an IDH1 and/or IDH2 mutation among 150 participants (NCT02481154). The study Start Date was June 2015. The estimated Study Completion Date is October 2018. The manufacturer planned to Initiate a perioperative ‘window’ study in the first half of 2018 with ivosidenib and AG-881 in approximately 45 low-grade glioma patients with the progressive disease to further investigate their effects on brain tumor tissue. This trial is recruiting. Patients will be randomized to either ivosidenib or AG-881 and treated for four weeks before previously scheduled surgery. An additional five patients will serve as a control arm. The study is designed to determine the amount of drug



penetration in the brain by confirming the magnitude of IDH target engagement as measured by 2HG levels in brain tumor tissue. It will assess the impact of IDH inhibition on differentiation and epigenetic profiles in tumor tissue and the safety of both molecules. The other one is NCT03343197, a phase 1, multicenter, randomized, and controlled, open-label, the perioperative study of AG-120 and AG-881 in subjects with recurrent, non-enhancing, IDH1 mutant, low-grade glioma. But like all other GBM, the results are still far from complete.

### Cholangiocarcinoma

Ivosidenib on the other hand almost completes the phase III trial, NCT02989857 on previously treated nonresectable or metastatic cholangiocarcinoma with an IDH1 mutation. It was presented at the recent European Society for Medical Oncology Congress (ESMO 2019) in Barcelona. It nearly doubled progression-free survival time, from a median of 1.4 to 2.7 months, meaning people randomly assigned to receive the drug were still alive without disease progression about twice if placebo recipients. Experts said the results could potentially change standard practice. Hence it appears that it will soon get approval for appears second line cholangiocarcinoma with a specific genetic mutation.

### Conclusion

Hence, though *IDH1* and 2 mutations were first detected in gliomas, the trial with glioma could not answer queries as satisfactorily as the trials on AML could do. This could be due to many factors like inherent role of such mutation in protection and better survival of GBM. This might have confused the calculation needed to present any concrete result with statistical sanction. As a result, more elaborate study with more patients are required. On the contrary it is marketed first for relapsed/refractory and later for newly diagnosed AML for straight cut favourable results. It seems is at least not until 2021 that they will be approved for GBM which may even more delayed in this time of turmoil due covid-19 pandemic.

### Compliance with Ethical Standards

Complied.

### Funding

Nil

### Conflict of Interest

Authors A & B declare that they have no conflict of interest.

### Ethical Approval

This article is a review and does not contain any studies with human participants or animals performed by any of the authors.

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