

April 2, 2019

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NCCN Guidelines Panel: AML

To Whom It May Concern,

As the NCCN Acute Myeloid Leukemia (AML) Panel reviews the NCCN Clinical Practice Guidelines in Oncology® (NCCN Guidelines®) for AML v.2.2019 and the associated Drugs and Biologics Compendium™, we have enclosed data relating to treatment with ivosidenib for your consideration:

- Data to support the use of ivosidenib in combination with induction chemotherapy in newly diagnosed patients with the IDH1 mutation eligible for intensive chemotherapy (not FDA approved)
- Data to support the use of ivosidenib in combination with SC azacitidine for the treatment of IDH1 mutated AML in previously untreated patients ineligible for intensive chemotherapy (not FDA approved).

The Tibsovo in combination with standard induction and consolidation therapy data were presented by Dr. Eytan Stein at ASH 2018 from a Phase 1 clinical study in patients with newly diagnosed AML.

As of the August 1, 2018 data cut-off, 60 newly diagnosed AML patients with mIDH1 received 500 mg of ivosidenib and standard induction chemotherapy (daunorubicin 60 mg/m²/day or idarubicin 12 mg/m²/day x 3 days with cytarabine 200 mg/m²/day x 7 days). After induction, patients received up to four cycles of consolidation chemotherapy while continuing ivosidenib (n=28). Patients who achieved a complete response (CR) or a complete response with incomplete neutrophil or platelet recovery (CRi/CRp) after consolidation could continue taking single agent ivosidenib daily until the end of the study which is up to two years from the last patient dosed.

The majority of ivosidenib-treated patients (70%) had de novo AML, while the remaining had secondary AML (sAML). In patients with sAML, 22% in the ivosidenib cohort had received prior hypomethylating agent therapy. The median age of patients was 62.5 years (range 24-76).

The frequency of Grade 3 or higher adverse events of interest, regardless of attribution, during the induction period were: differentiation syndrome (DS) in 3% (2/60) of patients, QT interval prolongation in 2% (1/60) of patients and blood bilirubin increased in 7% (4/60) of patients. The 30-day mortality rate was 5% and the 60-day mortality rate was 8%.

Seventeen out of 33 patients (52%) who discontinued ivosidenib treatment, proceeded to stem cell transplant.

An overall best response of CR+CRi/CRp was achieved in 80% (39/49) of efficacy evaluable patients. The CR+CRi/CRp rate for de novo patients was 91% (31/34) and 53% (8/15) for sAML patients. In a subset of

patients who achieved a CR or CRi/CRp, elimination of measurable residual disease (MRD) by flow cytometry was observed in 88% (15/17) of patients. In patients whose best response was CR or CRi/CRp, IDH1 mutation clearance by digital PCR was achieved in 41% (12/29) of patients. At the time of the data cut-off, the probability of survival at one-year was 79% and median overall survival (OS) was not yet estimable.

The ivosidenib with azacitidine combination data were presented by Dr DiNardo at the Acute Leukemias Meeting in Munich, Germany in February 2019. In this Phase 1b/2 study in patients previously untreated for AML, patients received Tibsovo or IDHIFA in combination with SC azacitidine. In Phase 1b, 23 patients received ivosidenib 500 mg daily in combination with SC azacitidine 75 mg/m²/day for 7 days in a 28 day cycle. Approximately 74% of patients had de novo AML and the majority had ECOG PS of 1 or 2. Median age was 76 years (range 61-88).

At a data cut-off of August 1, 2018, Grade 3/4 adverse events in the ivosidenib cohort in >20% of patients included thrombocytopenia (11/23), anemia (10/23), febrile neutropenia (10/23), neutropenia (6/23), and sepsis (5/23). There were 4 cases of DS; all DS events resolved and management included use of steroids and/or hydroxyurea for co-occurring leukocytosis. There were no ivosidenib discontinuations or deaths due to DS.

In the 23 ivosidenib and azacitidine treated patients evaluable for efficacy, the ORR was 78.3% (18/23).. Complete remission was achieved in 56.5% (13/23) of patients. CRi/CRp or MLFD was achieved in 13% (3/23) and 8.7% (2/23) of patients respectively. The median time to response was 1.8 months and median time to CR 3.5 months. Median durations of response and CR were not estimable yet. With a median duration of follow up of 9.5 months, the 12 month OS rate was 82%. The majority of patients with CR also had *IDH1* mutation clearance, as assessed by digital PCR.

On March 26th, 2019, the FDA granted Breakthrough Therapy designation for TIBSOVO[®] (ivosidenib) in combination with azacitidine for the treatment of newly diagnosed acute AML with an IDH1 mutation in adult patients who are ≥75 years old or who have comorbidities that preclude use of intensive induction chemotherapy.

The current Prescribing Information: Ivosidenib is an isocitrate dehydrogenase-1 (IDH1) inhibitor FDA-approved for the treatment of adult patients with relapsed or refractory acute myeloid leukemia (AML) with a susceptible IDH1 mutation as detected by an FDA-approved test.

Specific Changes:

Recommend the addition of ivosidenib in combination with standard induction chemotherapy (daunorubicin or idarubicin with cytarabine) to: AML-12

Recommend the addition of ivosidenib in combination with SC azacitidine to: AML-13

Rationale:

A Phase 1 clinical trial studied ivosidenib in combination with standard induction and consolidation therapy in patients with newly diagnosed AML (n=60). Of the 49 ivosidenib-treated patients analyzed

for clinical efficacy, 80% had a best response of CR+CRi/CRp (CR, 71%; CRi/CRp, 8%) as of August 2018. The median overall survival this population (n=60) is not yet estimable. After Induction Day 1, a 79% probability of 1-year survival was calculated. During the induction period, DS was observed in 2 patients (3%), QT interval prolongation was observed in 1 patient (2%), leukocytosis was not reported in any patients, and blood bilirubin increased in 4 patients (7%). The most common Grade ≥ 3 non-hematologic TEAE observed was febrile neutropenia (induction period, 62%; consolidation period, 36%).

This combination could provide a targeted treatment option for patients with frontline IDH1-mutated AML eligible for intensive chemotherapy.

In this Phase 1b/2 study in patients previously untreated for AML, patients received Tibsovo or IDHIFA in combination with SC azacitidine. In the 23 patients evaluable for efficacy, the ORR was 78.3% with a CR of 56.5%, CRi/CRp of 13% and MLFS of 8.7%. The median time to response was 1.8 months and median time to CR 3.5 months. Median durations of response and CR were not estimable yet. With a median duration of follow up of 9.5 months, the 12 month OS rate was 82%. At a data cut-off of August 1, 2018, Grade 3/4 adverse events in >20% of patients included sepsis, neutropenia, febrile neutropenia, anemia, and thrombocytopenia. There were 4 cases of DS; all DS events resolved and management included use of steroids and/or hydroxyurea for co-occurring leukocytosis. There were no ivosidenib discontinuations or deaths due to DS.

This combination could provide a targeted treatment option for patients with frontline IDH1-mutated AML ineligible for intensive chemotherapy.

The following articles are submitted in support of this proposed change. We would like to acknowledge the contributions of NCCN panel members who are also co-authors or co-contributors of some of these publications.

1. Stein EM, DiNardo CD, Fathi AT, et al. Ivosidenib or enasidenib combined with standard induction and consolidation chemotherapy in patients with newly diagnosed AML with an IDH1 or IDH2 mutation is safe, effective, and leads to MRD-negative complete remissions. Presented at the 60th American Society of Hematology (ASH) Annual Meeting 2018, Dec 1–4, San Diego, CA. Oral presentation #560. www.hematology.org
2. DiNardo C, Stein A, Stein E, et al. Safety and clinical activity of mutant IDH1 inhibitor ivosidenib (AG-120) in combination with azacitidine for newly diagnosed acute myeloid leukemia (ND-AML). Presented at the Acute Leukemias XVII Biology and Treatment Strategies 2019, Feb 24-27, Munich, Germany. Poster 40a.

We appreciate the opportunity to provide this additional information for consideration by the NCCN AML Panel. If you have any questions or require additional information, please do not hesitate to contact me.

Thank you for your time and consideration.

Sincerely,

Chris Bowden, MD
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Enclosures: Stein 2018, DiNardo 2019