Submitted by:
Dr. Gauthier Bouche, Director of Clinical Research
The Anticancer Fund
Boechoutlaan 221, B-1853 Strombeek-Bever, Belgium
Phone: +32 2 268 48 16
Email: gauthier.bouche@anticancerfund.org
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NCCN Guidelines Panel: Acute Myeloid Leukemia Panel

On behalf of the Anticancer Fund, a non-profit cancer research organization, I respectfully request the NCCN Acute Myeloid Leukemia Panel to review the enclosed data for inclusion of sorafenib in patients with *FLT3*-ITD acute myeloid leukemia (AML) after allogeneic hematopoietic stem-cell transplantation.

Specific Changes: We request the NCCN AML guidelines panel to consider:

- including on **page 30 (AML-4)** sorafenib maintenance for *FLT3*-ITD AML patients who underwent allogeneic hematopoietic stem-cell transplantation (initiated 30 to 60 days after transplantation until day 180 post-transplantation) with category 1.
- updating on **page 99 (MS-39)** the maintenance therapy section in the discussion to include the results of the 2 trials supporting sorafenib maintenance for *FLT3*-ITD AML patients who underwent allogeneic hematopoietic stem-cell transplantation .

FDA Clearance: Sorafenib is indicated for the treatment of unresectable hepatocellular carcinoma, advanced renal cell carcinoma, or recurrent/metastatic differentiated thyroid carcinoma. It is not currently approved for patients with *FLT3*-ITD acute myeloid leukemia after allogeneic hematopoietic stem-cell transplantation.

Rationale: Results in support of the changes are coming from 2 randomized clinical trials:

- Sorafenib-Flt3 AML-2015: an open-label phase 3 randomized trial in 202 patients with *FLT3*-ITD AML who received either maintenance sorafenib for 5 months (n=100) or no maintenance (n=102) after allogeneic hematopoietic stem-cell transplantation.
- SORMAIN: a placebo-controlled phase 2 randomized trial in 83 patients with *FLT3*-ITD AML in complete hematologic remission after hematopoietic stem-cell transplantation who received either maintenance sorafenib (n=43) or matching placebo (n=40) for 24 months.

The following articles are submitted in support of this proposed change.

1- **Sorafenib maintenance in patients with FLT3-ITD acute myeloid leukaemia undergoing allogeneic haematopoietic stem-cell transplantation: an open-label, multicentre, randomised phase 3 trial (Sorafenib-Flt3 AML-2015). Published in the Lancet Oncology**[1]
Results from this trial demonstrated a lower incidence of AML relapse and a greater overall survival in the sorafenib maintenance group compared to the control group. The primary endpoint, 1-year cumulative incidence of relapse, was 7.0% in the maintenance sorafenib arm vs. 24.5% in the non-maintenance arm (HR 0.25; 95% CI 0.11–0.57). Overall survival, a secondary endpoint, was improved, with 2-year OS rate of 82.1% vs. 62.0% (HR 0.48; 95% CI 0.27–0.86).

2- **Sorafenib Maintenance After Allogeneic Hematopoietic Stem Cell Transplantation for Acute Myeloid Leukemia With FLT3–Internal Tandem Duplication Mutation (SORMAIN). Published in the Journal of Clinical Oncology**[2]

Results from this trial demonstrated improved relapse-free survival and overall survival in the sorafenib maintenance group compared to the placebo group. The primary endpoint, relapse-free survival, was higher in the sorafenib arm than in the placebo arm (HR, 0.26; 95% CI 0.10–0.65) with 2-year rates of 85.0% vs 53.3%. Overall survival, a secondary endpoint, was improved, with 2-year OS rate of 90.5% vs. 66.2% (HR 0.24; 95% CI 0.08–0.74).

In both trials, sorafenib maintenance was not associated with significantly more toxicity than with placebo or no maintenance, though sorafenib dose modifications were frequent in both trials.

Thank you for your consideration of this request.

Sincerely,

Dr. Gauthier Bouche
Director of Clinical Research
The Anticancer Fund

References

1. Xuan L, Wang Y, Huang F, et al: Sorafenib maintenance in patients with FLT3-ITD acute myeloid leukaemia undergoing allogeneic haematopoietic stem-cell transplantation: an open-label, multicentre, randomised phase 3 trial. Lancet Oncol 2045:1–12, 2020
2. Burchert A, Bug G, Fritz L V., et al: Sorafenib Maintenance After Allogeneic Hematopoietic Stem Cell Transplantation for Acute Myeloid Leukemia With FLT3-Internal Tandem Duplication Mutation (SORMAIN). [Internet]. J Clin Oncol 38:2993–3002, 2020Available from: http://www.ncbi.nlm.nih.gov/pubmed/32673171