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NCCN Acute Myeloid Leukemia Guidelines Panel:

On behalf of Onyx Pharmaceuticals and Bayer HealthCare Pharmaceuticals, I respectfully request the NCCN Acute Myeloid Leukemia Guideline Panel to consider reviewing the enclosed data for the inclusion of sorafenib (Nexavar®) in the Acute Myeloid Leukemia treatment guidelines as a potential treatment option in the relapsed/refractory setting of *FLT3/ITD* positive AML, a condition associated with poor outcomes and limited treatment alternatives.

Specific Changes: Recommend the addition of sorafenib as an option for salvage therapy for patients with relapsed/refractory *FLT3/ITD+* AML.

FDA Clearance: Nexavar® (sorafenib) is a kinase inhibitor indicated for the treatment of unresectable hepatocellular carcinoma, advanced renal cell carcinoma, and locally recurrent or metastatic, progressive, differentiated thyroid carcinoma refractory to radioactive iodine treatment.[1] Sorafenib is currently not FDA approved for the treatment of AML.

Rationale: The presence of internal tandem duplication (ITD) mutations in the *FLT3* gene is associated with an increased risk of relapse and a shorter overall survival (OS) in AML patients. Agents targeting the FLT-3 kinase have shown promising activity in patients with AML and mutated *FLT3.* Sorafenib is an orally active small molecule kinase inhibitor with potent activity against FLT3 and the raf/ERK/MEK pathway.[2, 3] Sorafenib has demonstrated activity in AML patients in both the frontline and relapsed setting, either as monotherapy or combined with chemotherapy. In the frontline/induction setting, the results have been mixed and responses were of limited duration.[4-7]

The attached table outlines several studies (Phase I/II, Compassionate Use, and Retrospective design) evaluating the use of sorafenib, as monotherapy or in combination with chemotherapy, in patients with relapsed or refractory AML and *FLT3*-ITD mutation.[8-17] The findings can be summarized as follows:

- Sorafenib treatment leads to a high response rate in relapsed or refractory *FLT3*-ITD positive AML patients.
- The duration of response to sorafenib varies and may be related to the initial degree of *FLT3* inhibition.
- Activity seen in patients who have failed multiple prior therapies, including prior treatment with *FLT3*-ITD inhibitors.

- Sorafenib combination therapy with chemotherapy may improve duration of response versus monotherapy.
- High response rates enabled some patients to proceed to potentially curative HSCT.

We appreciate your review and consideration of this recommendation. Should you have any questions regarding the content of this letter, please do not hesitate to contact me.

Sincerely,

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Author / Regimen / Pub Type	Study Phase/ Line of Therapy	N	*FLT3*-ITD Mutation	Main Study Findings	Overall Outcome	Comments
Andreef[8] ***SOR/plerixafor/ G-CSF*** **ASH 2012 Oral Presentation**	Ph I – RR[a]	15	+	• ORR: 73% (CR/CRp 27%) • No CR/CRp in *FLT3*-ITD+D835 mutations (only PRs) • 18% of responders and 100% of non-responders pretreated with *FLT3*-ITD inhibitors	Positive	• High ORR despite 47% received prior *FLT3*-ITD inhibitors • Disruption of stroma-leukemia interactions may augment SOR efficacy
Sayer[9] ***SOR/Vorinostat*** **ASH 2010 Poster**	Ph I – RR	15	+/- (+=20%)	• All 3 $FLT3^{+}$ pts achieved PR or VGPR • Pts with response had p52NFκB depletion at day 3/4	Positive	• All responders had p52NFκB depletion • BTZ also inhibits p52NFκB and is being tested with SOR/VOR in high-risk AML
Inaba[10] ***SOR/ara-C/ clofarabine*** **Manuscript *(JCO 2011)***	Ph I – RR (pediatrics)	12	+/- (+=42%)	• MTD: SOR 150 mg/m^2 BID + clofarabine/ara-C • 6 pts achieved CR (3 $FLT3^{+}$ and 3 $FLT3^{-}$) • All pts experienced HFSR	Positive	• SOR active regardless of *FLT3* status • Increased AEs due to SOR converting to active metabolite faster in pediatric pts
Crump[11] ***SOR monotherapy*** **Manuscript *(Leukemia & Lymphoma 2010)***	Ph I – RR	42 (38 AML)	+/- (+=33%[b])	• The only response observed was a pt with *FLT3*-ITD^{+} AML who achieved CR • 6 pts achieved improvement or clearance of blasts	Neutral	• RP2D: SOR 300 mg BID continuously • Testing in combination with chemotherapy and in $FLT3^{+}$ warranted
Ravandi[12] ***SOR/AZA*** **ASH 2013 Poster**	Ph II – RR[a] (13 pts previously untreated) Med age = 65 yrs	57	+/- (+=93%)	• Overall CR/Cri/PR rate = 44% (previously untreated = 62%; relapsed = 39%) • CR = 8pts (14%) • Cri = 16pts (28%) • PR = 1pt (2%) • Med duration of CR/Cri = 2.4mo • Med OS = 6.3mo • Med OS in 25 responding pts = 12.4mo	Positive	• 7 patients proceeded to allogeneic stem cell transplant • Combo of SOR+AZA is effective for the treatment of patients with AML and *FLT3*-ITC

Author / Regimen / Pub Type	Study Phase/ Line of Therapy	N	*FLT3*-ITD Mutation	Main Study Findings	Overall Outcome	Comments
Man[13] ***SOR monotherapy*** **Manuscript** ***(Blood 2012)***	Ph II – RR	13	+	• CRi/nCRi:92% • Of the 12 responders, 3 still in remission (2 after allogeneic HSCT after Cri) • 9 pts lost response despite cont SOR tx • Preclinical model showed emergence of D835 mutation as mechanism of SOR resistance	Positive	• SOR led to initial favorable responses; however pts eventually lost response to SOR despite continued *FLT3* signaling suppression • High RR enabled 2 pts to proceed to potentially curative HSCT
Metzelder[14] ***SOR monotherapy*** **Manuscript** ***(Blood 2009)***	Compassionate Use – RR	6	+	• Pts received SOR before (n=3) or after (n=3) allo HSCT • SOR induced CMRs in relapsed pts following allo HSCT	Positive	• Prophylactic SOR may be effective in RR AML after allo HSCT – trials warranted
Metzelder[15] ***SOR monotherapy*** **Manuscript** ***(Leukemia 2012)***	Retro – RR	65	+	• CR/CRi: 3%/20% (all but 1 pt achieved ≥ HR) • TTF (CT vs allo HSCT): 4.5 mo vs 6.5 mo (*P*=.0305) • SOR resistance (CT vs allo HSCT): 47% vs 38%	Positive	• RR AML after prior allo HSCT developed SOR resistance less frequently and later vs pts w/o prior allo HSCT • SOR may synergize with allo immune effects to induce durable CR
Sharma[16] ***SOR ± chemo*** **Manuscript** ***(Biol Blood Marrow Transplant 2011)***	Retro – RR (after allo HSCT)	16	+	• No patient achieved CR (poor prognosis population) • 2 pts received 2nd HSCT, but both relapsed within 3 mo	Negative	• SOR not effective for *FLT3*$^{+}$ AML post HSCT – prophylactic use may be useful
Pollard[17] ***SOR monotherapy*** **ASH 2013 Poster**	Retro – RR (SOR following allo HSCT) Pediatrics	13	+	• 10/13 pts(77%) remain alive and 7/13 (54%) are disease free • Of 7 pts in CR, med OS = 3.6 yrs from HSCT and 6/7 are off SOR therapy	Positive	• Toxicity resulted in reduction or temporary DC of SOR tx in 8/13 pts (61%), but all pts tolerated retrial of drug at same or reduced dose • Of interest is positive outcome in pts who received SOR for MRD in peri-transplant period

[a] Or patients unsuitable for standard induction chemotherapy.; [b] 9 of 27 pts evaluable for *FLT3* status were *FLT3*$^{+}$.

Bayer HealthCare

ONYX PHARMACEUTICALS
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