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NCCN® Guidelines Panel: Melanoma

Dear NCCN Guidelines Panel,

On behalf of Array BioPharma, I respectfully request the NCCN® Melanoma Panel to review the enclosed data on the use of the combination treatment of encorafenib (BRAF inhibitor) plus binimetinib (MEK inhibitor) for the treatment of patients with metastatic or unresectable melanoma with a *BRAF V600* mutation.

Specific Changes: In section ME-H, I respectfully request you consider recommending the combination of encorafenib/binimetinib as a category 1 option for systemic therapy of metastatic or unresectable disease in the following lines of therapy:

- First-line targeted therapy if *BRAF V600* activating mutation is present
- Second-line or subsequent targeted therapy if *BRAF V600* activating mutation is present

FDA Clearance: The FDA is currently reviewing the New Drug Application for *encorafenib (*BRAFTOVI™*) and binimetinib (*MEKTOVI®) for use in combination for the treatment of patients with unresectable or metastatic melanoma with a BRAF V600E or V600K mutation as detected by an FDA-approved test. The PUDFA date is 30 June 2018.

Rationale:

The pivotal COLUMBUS phase III study, met its primary endpoint showing the combination of encorafenib 450 mg daily and binimetinib 45 mg BID demonstrated longer progression-free survival (PFS) than single-agent vemurafenib (HR=0.54; 95%CI 0.41-0.71, p<0.0001).[1] Median PFS was longer for the combination (14.9 months) than either vemurafenib (7.3 months) or encorafenib (9.6 months).[1] Recently presented data also showed that the combination prolonged overall survival relative to either single agent[2]. Of note vemurafenib demonstrated a response rate, median PFS and median OS consistent with other pivotal trials where it was used as a control, thus validating it as an internal control and providing an external benchmark.[1,2]
In COLUMBUS, the combination of encorafenib and binimetinib showed the longest median PFS and OS (33.6 months) observed to date with any BRAF/MEK inhibitor combination.[2]

A detailed description of the safety and tolerability of encorafenib and binimetinib is available in published results of the primary analysis of the trial.[1] The most common adverse reactions (≥25%, all grades) for

encorafenib and binimetinib in COLUMBUS Part 1 were fatigue, nausea, diarrhea, vomiting, abdominal pain, and arthralgia.[1]

The following resources are being submitted in support of the proposed change to the NCCN Melanoma guidelines:

Encorafenib/Binimetinib (combination)

1. Dummer R, et al. Encorafenib plus binimetinib versus vemurafenib or encorafenib in patients with *BRAF*-mutant melanoma: a multicentre, open-label, randomised phase 3 trial. *Lancet Oncol.* 2018 May;19(5):603-615.
2. Dummer R, et al. Overall survival in COLUMBUS: A phase 3 trial of encorafenib (ENCO) plus binimetinib (BINI) vs vemurafenib (VEM) or ENCO in *BRAF*-mutant melanoma. J Clin Oncol 36, 2018 (suppl; abstr 9504); presented at ASCO 2018 Annual Meeting; Chicago, IL; 1-5 June 2018.
3. Koelblinger P, Thuerigen O, and Dummer R. Development of encorafenib for BRAF-mutated advanced melanoma. *Curr Opin Oncol.* 2018;30:125-133. doi:10.1097/CCO.0000000000000426. [Epub ahead of print].
4. Koelblinger P, Dornbierer J, Dummer R. A review of binimetinib for the treatment of mutant cutaneous melanoma. *Future Oncol* 2017;13:1755–1766.

Encorafenib (single-agent)

5. Delord JP, et al. Phase I dose-escalation and -expansion study of the BRAF inhibitor encorafenib (LGX818) in metastatic *BRAF*-mutant melanoma. *Clin Cancer Res.* 2017;23:5339–5348.

Binimetinib (single-agent)

6. Bendell JC, et al. A phase I dose-escalation and expansion study of binimetinib (MEK162), a potent and selective oral MEK1/2 inhibitor. *Br J Cancer.* 2017;116:575–583.
7. Ascierto PA, et al. MEK162 for patients with advanced melanoma harbouring NRAS or Val600 BRAF mutations: a non-randomised, open-label phase II study. *Lancet Oncol.* 2013;14:249–256.

We thank you for your consideration of this request.

Sincerely,

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