Genentech
A Member of the Roche Group

Submitted by:
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NCCN Guidelines Panel: Melanoma

Dear NCCN Melanoma Panel:

On behalf of Genentech, Inc., enclosed is notification of the FDA approval for Tecentriq® (atezolizumab) in combination with Cotellic® (cobimetinib) and Zelboraf® (vemurafenib) for the treatment of BRAF^{V600} mutation-positive advanced or metastatic melanoma.[1,2]

Request:
Please consider for inclusion the FDA approval and enclosed published results on the use of Tecentriq® (atezolizumab) in combination with Cotellic® (cobimetinib) and Zelboraf® (vemurafenib) for the treatment of BRAF^{V600} mutation-positive advanced or metastatic melanoma who have not received prior systemic treatment in the metastatic setting (page ME-I [1 of 7] in the NCCN Cutaneous Melanoma Guideline).[3,4]

Rationale:[2-4]
IMspire150 was a Phase III, double blind, placebo-controlled study conducted to evaluate the addition of Tecentriq to Cotellic and Zelboraf for the treatment of previously untreated patients with BRAF^{V600} mutation-positive advanced or metastatic melanoma. Patients were randomized in a 1:1 ratio to receive Tecentriq, Cotellic, and Zelboraf (Tecentriq group), or to receive placebo, Cotellic, and Zelboraf (control group).

The primary efficacy endpoint was investigator-assessed (INV) progression-free survival (PFS). Key secondary endpoints included overall survival (OS) and duration of response (DOR).

Efficacy[2,3]
In total, 514 patients were randomized to either the Tecentriq group (n=256) or the control group (n=258).

- At a median survival follow-up of 18.9 months, the addition of Tecentriq to Cotellic and Zelboraf significantly prolonged median PFS (INV) from 10.6 months to 15.1 months; HR=0.78 (95% CI, 0.63-0.97); p=0.0249.
- Interim analysis showed a median OS of 28.8 months, with fewer deaths in the Tecentriq group vs the control group (36% vs 43%, respectively; HR=0.85 (95% CI 0.64-1.11); p=0.2310. However, at this pre-specified analysis at the time of primary analysis of PFS, the OS data was still immature.
- Overall response rates were similar between the Tecentriq (66%; 95% CI, 60-72) and control group (65%; 95% CI, 59-71). Rates of complete response, partial response, and stable disease were also similar between both arms.
- The DOR was prolonged for patients in the Tecentriq group (20.4 months) vs the control group (12.5 months).

Treatment options for patients with CNS metastases remain a large unmet need in melanoma. An exploratory analysis by Ascierto et al. showed that the addition of Tecentriq to Cotellic plus Zelboraf is associated with lower cumulative incidence and lower rates of development for CNS metastases in patients who did not have CNS metastases at baseline.[4] The observed risk reduction for CNS metastases is consistent with the overall benefit seen for the Tecentriq group vs the control group in IMspire150, and the landmark CNS metastases incidence rates in both groups were better than the historical benchmark.[4]

Safety[2,3]
The safety profile of Tecentriq plus Cotellic and Zelboraf was consistent with known safety risks of the individual agents.

- The incidence of treatment-related grade 3/4 AE was 79% and 73% in the Tecentriq and control group arms, respectively. Adverse reactions leading to discontinuation of Tecentriq occurred in 21% of patients in the Tecentriq group.
- Grade 5 AEs were reported in seven patients within each group and most events were considered unrelated to treatment, with no trend or pattern identified. AE's leading to death in the Tecentriq group were hepatic failure, fulminant hepatitis, sepsis, septic shock, pneumonia, and cardiac arrest.
- Grade 3 or 4 treatment-related adverse events occurring in ≥ 10% of patients in either arm, and at a higher incidence (≥2% between arm difference) with Tecentriq group vs the control group were rash, pruritis, photosensitivity reaction, fatigue, pyrexia, edema, hepatotoxicity, nausea, stomatitis, musculoskeletal pain, hypothyroidism and hyperthyroidism, infusion-related reactions, pneumonitis, and hypertension.

FDA Clearance:[2,5-6]

- Tecentriq in combination with cobimetinib and vemurafenib is FDA-approved for the treatment of patients with BRAF V600 mutation-positive unresectable or metastatic melanoma. Please refer to the product prescribing information for the full FDA-approved indications and safety information of Tecentriq, available at:
  - https://www.gene.com/download/pdf/tecentriq_prescribing.pdf
- Cotellic® (cobimetinib) is FDA-approved for the treatment of patients with unresectable or metastatic melanoma with a BRAF V600E or V600K mutation, in combination with vemurafenib. Please refer to the product prescribing information for the full FDA-approved indication and safety information of Cotellic, available at:
  - https://www.gene.com/download/pdf/cotellic_prescribing.pdf
- Zelboraf® (vemurafenib) is FDA-approved for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E mutation as detected by an FDA-approved test, and for the treatment of patients with Erdheim-Chester Disease with BRAF V600 mutation. Please refer to the product prescribing information for the full FDA-approved indication and safety information of Zelboraf, available at:
  - https://www.gene.com/download/pdf/zelboraf_prescribing.pdf

Thank you for your consideration and I hope this information is helpful to you. If you have any questions, please contact us at the phone number and email address provided above.

Respectfully submitted,
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References

1. *FDA Approves Genentech's Tecentriq plus Cotellic and Zelboraf for People with Advanced Melanoma* [Press Release]. Genentech, Inc; July 30, 2020. Available at: https://www.gene.com/media/press-releases/14868/2020-07-30/fda-approves-genentechs-tecentriq-plus-c.
2. Tecentriq [package insert]. Genentech, Inc; South San Francisco, CA. 2020.
3. Gutzmer R, Stroyakovskiy D, Gogas H, et al. Atezolizumab, vemurafenib, and cobimetinib as first-line treatment for unresectable advanced BRAF V600 mutation-positive melanoma (IMspire150): primary analysis of the randomized, double-blind, placebo-controlled, phase 3 trial. Lancet. 2020;395:1835-44. Available at: https://pubmed.ncbi.nlm.nih.gov/32534646/
4. Ascierto PA, Robert C, Lewis KD, et al. Time to central nervous system (CNS) metastases (mets) with atezolizumab (A) or placebo (P) combined with cobimetinib (C) + vemurafenib (V) in the phase III IMspire150 study. J Clin Oncol. 2020;38:suppl;abstr 10023. Abstract available at: https://ascopubs.org/doi/abs/10.1200/JCO.2020.38.15_suppl.10023
5. Cotellic [package insert]. Genentech; South San Francisco, CA. 2018.

6. Zelboraf [package insert]. Genentech; South San Francisco, CA. 2017.