



Submitted by:
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NCCN Guidelines Panel: Hepatobiliary Cancers

Dear NCCN Guidelines Panel:

On behalf of Genentech, Inc., enclosed for your review are results from the Phase III IMbrave150 study evaluating Tecentriq® (atezolizumab) in combination with Avastin® (bevacizumab) for the treatment of unresectable hepatocellular carcinoma (HCC).¹

Request:

Consider the inclusion of Tecentriq in combination with Avastin (T+A) as a treatment option for patients with unresectable HCC who have not received prior systemic therapy.

Rationale:

Treatment options for patients with unresectable HCC remain a tremendous unmet medical need. IMbrave150 is a global Phase III, multicenter, open-label study in 501 patients with unresectable HCC who have not received prior systemic therapy. Patients were randomized 2:1 to receive the combination of T+A or sorafenib.¹

Co-primary endpoints were overall survival (OS) and progression-free survival (PFS) by independent review facility (IRF) per RECIST 1.1. Secondary endpoints included overall response rate (ORR), time to progression (TTP), duration of response (DoR), safety and patient reported outcomes.

- A total of 501 patients were randomized to receive either T+A (n=336) or sorafenib (n=165). 77% of patients in the T+A arm and 73% in the sorafenib arm had macrovascular invasion (MVI) and/or extrahepatic spread (EHS) present at baseline. 38% of patients in the T+A arm had AFP \geq 400 ng/mL at screening. Patients were Child-Pugh class A in both arms. Median duration of follow-up was 8.6 months.
- IMbrave150 met both of its co-primary endpoints demonstrating statistically significant and clinically meaningful improvements in OS and PFS compared with sorafenib.
 - OS HR, 0.58 (95% CI: 0.42–0.79); median OS NE for T+A vs 13.2 months for sorafenib; $P=0.0006$
 - PFS HR, 0.59 (95% CI: 0.47–0.76); median PFS 6.8 months for T+A vs 4.3 months for sorafenib; $P<0.0001$
- ORR by IRF RECIST 1.1 was 27% in the T+A arm and 12% in the sorafenib arm ($P<0.0001$) and responses were durable with 87% of patients on T+A having an ongoing response at time of analysis (median DoR NE).

The safety profile of Tecentriq and Avastin was consistent with previously reported safety risks of the individual medicines. No new safety signals were identified.¹

- Grade 3-4 treatment related adverse events (AEs) were noted in 36% of patients in the T+A arm and 46% in the sorafenib arm. 16% and 10% of AEs lead to study withdrawal in each arm, respectively.



- All-grade AEs occurring in $\geq 10\%$ of patients in either arm with $> 5\%$ difference between arms include: diarrhea, palmar-plantar erythrodysesthesia, decreased appetite, hypertension, abdominal pain, alopecia, asthenia, pyrexia, increased ALT, proteinuria, and infusion-related reactions.
- Treatment with T+A resulted in a 7.6-month delay in median time to deterioration of patient-reported quality of life (11.2 months compared to 3.6 months in the sorafenib arm, HR 0.63 [95% CI 0.46–0.85]).

FDA Clearance:

The U.S. Food and Drug Administration granted Breakthrough Therapy Designation for Tecentriq in combination with Avastin as first-line treatment for patients with advanced or metastatic HCC.^{2,3}

- Tecentriq and Avastin are not FDA-approved for the treatment of HCC. Please refer to the product prescribing information for the full FDA-approved indications and safety information of Tecentriq and Avastin, available at:
 - <https://www.gene.com/medical-professionals/medicines/tecentriq>
 - <https://www.gene.com/medical-professionals/medicines/avastin>

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We appreciate your review and consideration.

Sincerely,
Patrice Esser, PharmD, MPH

References:

1. Ann-Lii Cheng, Shukui Qin, Masafumi Ikeda et al. Atezolizumab + bevacizumab vs sorafenib in patients with unresectable hepatocellular carcinoma: Phase 3 results from IMbrave150. Presented at the European Society for Medical Oncology Asia Congress in Singapore; November 22-24, 2019. Oral Presentation.
2. Genentech, Inc. (2018, July 17). *FDA Grants Breakthrough Therapy Designation for Genentech's TECENTRIQ in Combination With Avastin as First-Line Treatment for Advanced or Metastatic Hepatocellular Carcinoma (HCC)* [Press release]. Retrieved from <https://www.gene.com/media/press-releases/14736/2018-07-17/fda-grants-breakthrough-therapy-designat>
3. Genentech, Inc (2019, Nov 22). *Genentech Presents Pivotal Data Demonstrating Tecentriq in Combination With Avastin Improves Overall Survival in People With the Most Common Form of Liver Cancer* [Press release]. Retrieved from <https://www.gene.com/media/press-releases/14824/2019-11-22/genentech-presents-pivotal-data-demonstr>