Systemic Therapy for Advanced Hepatocellular Carcinoma Algorithm

**Patients with advanced hepatocellular carcinoma**

- Child-Pugh class A and ECOG PS 0-1 → No
  - A cautious approach to systematic therapy in advanced HCC patients with Child-Pugh class B and good performance status is recommended

- Yes
  - First-line systemic therapy with atezo+bev or durva+treme?
    - Yes
      - First-line systemic therapy with atezo+bev or durva+treme may be offered
    - No
      - Patient with contraindications to atezo+bev or durva+treme?
        - Yes
          - Progression with first-line atezo+bev?
            - Yes
              - Second-line therapy with a TKI (i.e., sorafenib, lenvatinib, or cabozantinib) or ramucirumab (for AFP ≥400 ng/mL) may be offered
            - No
              - Progression with second-line therapy?
                - Yes
                  - Third-line therapy may be considered, using one of the agents listed previously that has a non-identical mechanism of action with previously received therapy
                - No
                  - Atezo+bev

- No
  - Progression with first-line durva+treme?
    - Yes
      - Second-line therapy with a TKI (i.e., sorafenib, lenvatinib, or cabozantinib) or atezo+bev may be offered
    - No
      - Progression or intolerable toxicity with first-line TKI?
        - Yes
          - Second-line therapy with another TKI (cabozantinib or regorafenib), ramucirumab (AFP ≥400 ng/mL), nivo+ipi, or durvalumab may be recommended for appropriate candidates.
          - Atezo+bev or durva+treme may be considered for patients who did not have access to these therapies in the first-line setting and do not have contraindications.
          - ICIs pembrolizumab or nivolumab may be offered to appropriate patients
        - No
          - Durva+treme

Notes.

1. The target population includes patients who are no longer candidates for surgical or liver-directed therapies, i.e. patients with characteristics such as multifocal and/or infiltrative disease within the liver, vascular invasion or extrahepatic spread.
2. Treatment options should be discussed within a multidisciplinary team.
3. Patients in the IMbrave150 trial of atezo+bev were required to have undergone esophagogastroduodenoscopy (EGD) within 6 months of trial initiation and to have received treatment for esophageal varices when necessary.
4. Considerations include underlying liver function, bleeding risk, presence of portal hypertension, extent of extrahepatic spread, tumor burden, and major vascular invasion.
5. While there is currently no published evidence to support a recommendation for durva+treme, the ASCO Advanced HCC Expert Panel agreed that this option may be considered following first-line treatment with atezo+bev.
6. There is no data available to select patients for atezo+bev vs. second-line therapy with a TKI.
7. Pembrolizumab or nivolumab are reasonable options that may be considered for appropriate candidates following first-line therapy with sorafenib or lenvatinib.

Abbreviations. AFP, alpha fetoprotein; atezo+bev, atezolizumab+bevacizumab; durva+treme, durvalumab + tremelimumab; ECOG PS, Eastern Cooperative Oncology Group performance status; HCC, hepatocellular carcinoma; ICI, immune checkpoint inhibitor; nivo+ipi, nivolumab + ipilimumab; TKI, tyrosine kinase inhibitor.

This algorithm is derived from recommendations in Systematic Therapy for Advanced Hepatocellular Carcinoma: ASCO Guideline Update. This is a tool based on an ASCO Guideline and is not intended to substitute for the independent professional judgment of the treating physician. Practice guidelines do not account for individual variation among patients. This tool does not purport to suggest any particular course of medical treatment. Use of the guideline and this tool are voluntary.