



(1) Esophageal varices screening and treatment prior to starting treatment is recommended. Although no prior studies compared atezolizumab/bevacizumab versus lenvatinib, the results of the REFLECT trial suggest that sorafenib and lenvatinib are comparable.

(2a) Patients who place a higher value on delayed radiologic disease progression and lower value on the increase in adverse events (both serious and leading to discontinuation of the drug) may reasonably choose Lenvatinib.

(2b) Patients who place a higher value on blood pressure control and a lower value on the adverse skin reactions would reasonably select sorafenib.

(2c) It should be noted that lenvatinib has not been studied in patients with invasion of the main portal vein and thus may not be appropriate for this population.

(3a) Patients who place a higher value on adverse effects associated with any of the second-line therapies (regorafenib, cabozantinib, pembrolizumab, or ramucirumab) and lower value on the reduction in mortality (1.2 to 2.8 months) may reasonably decline second-line therapies.

(3b) Regorafenib should not be used in patients who did not tolerate sorafenib due to toxicity.

(3c) Patients with main portal vein invasion or inferior vena cava or cardiac involvement of HCC on the basis of imaging were not studied.

(3d) No high-quality direct evidence is available for either atezolizumab/bevacizumab, sorafenib, or lenvatinib as second-line therapies. However, patients who put a high value on the uncertain benefit of atezolizumab/bevacizumab, sorafenib, or lenvatinib as second-line therapies and low value on their adverse events could reasonably select to use either atezolizumab/bevacizumab, sorafenib, or lenvatinib as second-line therapies.